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The largest dosimetry organizations

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► ***Review article***

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ABSTRACT

Radiotherapy has been the modality for treating cancer patients worldwide for more than 100 years. Radiation dose to patients is delivered through different techniques using high-energy photon beams generated by the linear accelerators. Radiotherapy techniques are developing at a speed never seen before. For continuous improvement, safe and effective radiotherapy delivery requires implementing adapted quality assurance (QA) programs and integral quality management (QM) systems. A key step in any QA program is the dosimetry audit. It provides an effective tool to improve the accuracy of patients' treatments. In the global panorama, dosimetry audit programs are conducted by various institutions. Still, the largest of them is the International Atomic Energy Agency (IAEA) in Vienna, Austria, the Imaging and Radiation Oncology Core (IROC-H) Houston QA Center in the USA, and EQUAL (European Quality Laboratory) Laboratory in the framework of the ESTRO (European Society for Therapeutic Radiology and Oncology) ESTRO – EQUAL Laboratory in Villejuif Cedex, France.

INTRODUCTION

The authors will review the dosimetry audits of radiation therapy organized by leading centers worldwide regarding methods, tools, and checked beams. The review is based on the documentary method-systematization and analysis of information from international and contemporary literary sources.

Dosimetry audits play an essential role in developing safety in the clinical specialty of radiotherapy. Dosimetry audits have proved to be a valuable tool for improving radiotherapy quality. National and large-scale international audits can define, maintain, and improve quality standards. They also have the potential to identify errors and problems causing harm to patients. The most common mistakes or pitfalls detected during the audits, which contribute to the inaccuracy of reference dosimetry for photon beams, are given below and organized by the frequency of their occurrence.

Lack of recent beam calibration and radiation output check; Use of solid phantoms (e.g., PMMA) instead of water for reference dosimetry; Inconsistencies in the determination of Percentage Depth Dose (PDD) curves and the PDD at effective point of measurement, PDD (10) or PDD (5); Incorrect application of temperature correction factor; i.e., room air temperature is used instead for the water temperature; uncalibrated thermometers, especially electronic ones; Application of uncertain or incorrect correction factors for polarity & ion recombination; Lack of recent calibration of dosimetry equipment (ionization chambers and electrometer); Lack of barometers; uncalibrated barometers, especially electronic ones; incorrect interpretation of pressure (e.g., absolute or relative to sea level); Mechanical performance of EBRT unit, especially in respect to the SSD indication and laser alignment and field size; For the Co-60 units, there is a lack of dosimetry output measurements; The output is based on the Co-60 source decay data; Inappropriate or incorrect application of the dosimetry protocol, especially in the first DA rounds; Errors and bugs in home-made dosimetry algorithms /software/ calculations [(1)].

Remote dosimetry audit motivates centers to modernize and develop new techniques. It creates confidence that radiotherapy is planned accurately and that the absorbed dose in patients matches the prescribed one. Dosimetry intercomparison, i.e., the

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physical process of comparing measured doses with predicted doses, is usually a part of the dosimetry audit, which implies a broader framework within which this is used as a tool [2].

The dosimetry audit appeared on the world scene in the field of radiation dosimetry more than 50 years ago. The audit aims to ensure high-quality and safe radiation treatment for millions of patients with oncological diseases worldwide. It begins as a remote (postal) dosimetry audit. For its full implementation, it is of utmost importance to choose a dosimetry method where the dosimeters can be sent by mail, retain the signal for a specific time, and be stable, accessible, and cheap. The dosimeters that are considered suitable for remote dosimetry are the Thermo Luminescent Dosimeters (TLDs). The remote dosimetry audit is based on measurements performed with TLDs sent by postal mail to the participating center to be irradiated on the axis in reference conditions and conditions close to clinical conditions for photon and electron beams. The maximum acceptable discrepancy between the dose stated by the radiotherapy center and the dose evaluated by the Dosimetry Audit Organizations is ± 5 %. Over the time, other detectors are used, such as Optically Stimulated Luminescent Dosimeters (OSLDs), Radio Photo Luminescence Dosimeters (RPLDs), and RadioChromic Films (RCFs), which are distributed to the radiotherapy centers by post.

For the first time, the article will summarize the activities in the field of remote dosimetry audit of the Largest Dosimetry Organizations and share knowledge, information, and achievements among the professional radiation oncology community (medical physicists and radiation oncologists) around the world.

DIFFERENT TYPES OF DOSIMETRY SYSTEMS

Thermo-luminescence dosimeters (TLDs)

Thermo-luminescence dosimeters (TLDs) are a well-established technique available for decades. Because of their tissue equivalence, the TLDs most commonly used in medical applications are LiF: Mg, Ti, LiF: Mg, Cu,P, and 7LiF: Na, Mg, Ti, TLD 937. The TLD can come in many forms, such as powder, chips, microchips, rods, or ribbons (Figure 1). They are offered on the market by the USA Company Thermo Fisher Scientific and the European French Company Philitec.

TLDs are made of specific crystals that can absorb and store the energy of ionizing radiation, which can be released as visible light during heating. The main form of thermo-luminescent dosimeters used for dosimetry audits is powder LiF: Mg, Ti (TLD-100) [1-8].

The TLD reader system consists of the thermoluminescence light emission and convert it into an electrical system consists of a planchet for placing and heating the TLD, a PMT to detect signal linearly proportional to the detected photon fluence and an electrometer for recording the PMT signal as a charge or current (figure 2).

Figure 1. Thermoluminescent dosimeters (TLDs) in different forms.

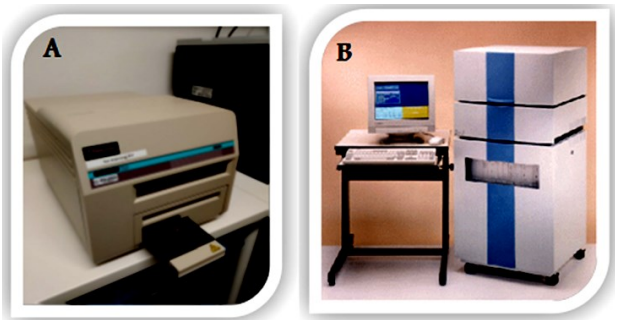

Figure 2. TLD readers: Harshaw 3500 manual reader (Thermo Fisher Scientific, USA) **(A)**, and PCL3 automatic reader (Fimel, France, Europe) **(B)**.

The TLD system used in remote dosimetry systems is the dosimeters in plastic capsules filled in with TLD-100 powder (LiF: Mg,Ti) (figure 3).

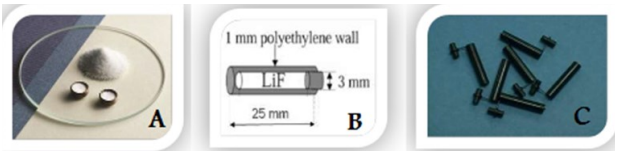

Figure 3. TLD -100 in the form of powder **(A)**, capsule' **(B)**, and black plastic capsules **(C)**.

The correct preparation of TLD is essential as its sensitivity depends on the annealing procedure, which should be carefully followed. Before TLD powder is used for dose measurements, it undergoes an annealing process of 1 h at 400°C, followed by fast cooling for 20 min and 24 h at 80°C. After the annealing, TLD powder is stored in dark glass containers to avoid light exposure. The powder is sieved to result in grain sizes between 80 µm - 200 µm to ensure that the powder consists of homogenous grains. Plastic capsules of inner dimensions 20 mm long and 3 mm in diameter are filled with 165 mg of powder. All dosimeters prepared from the same lot of powder are assumed to have the same sensitivity. One TLD capsule allows the preparation of four powder samples, dispensed into stainless steel cupels that are loaded into the Reader. Up to 85 cupels can be read in one session, which takes about 45 min. The TLD system and the readout procedure have been described previously [3].

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The peaks in the glow curve may be correlated with trap depths responsible for thermoluminescence emission. The main dosimetric peak of the LiF: Mg, Ti glow curve between 180ºC and 260ºC is used for dosimetry. The peak temperature is high enough not to be affected by room temperature and still low enough not to interfere with black body emission from the heating planchet. The total thermoluminescence signal emitted (i.e., the area under the appropriate portion of the glow curve) can be correlated to the dose through proper calibration. Good reproducibility of heating cycles during the readout is essential for accurate dosimetry.

TLDs must be calibrated before they are used (thus, they serve as relative dosimeters). A few correction factors for energy, fading, and dose-response non-linearity must be applied to derive the absorbed dose from the thermoluminescence readings [4-7].

Optically stimulated luminescence dosimeters (OSLDs)

The OSLDs work similarly to TLDs, with the difference that light instead of heat is used to release the energy trapped during the irradiation [9-16]. When OSLDs are irradiated, the electron-hole pairs are produced and trapped at the localized energy levels. The light from OSLDs is emitted when the trapped charges are released when exposed to the laser light or a light-emitting diode (LED) source, and they recombine. Dosimeters made of Al_2O_3:C are used for audit purposes (figure 4).

The OSLDs are produced as nanoDot™ by European Company Landauer in France, and the OSLD reader – microSTARii (figure 5).

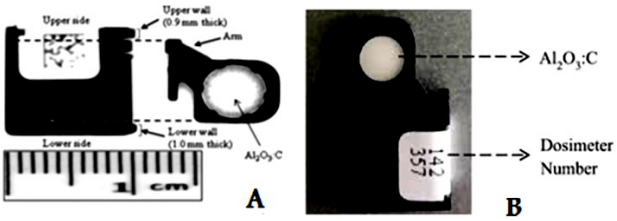

Figure 4. NanoDot dosimeter and its plastic case (10×10×2 mm). The attaching arm allows the Al2O3:C detector to provide from its case for readout or bleaching. The upper and lower sides of the plastic are sealed with 0.9 and 1.0 mm walls, respectively **(A)** and a general view of OSLD **(B)**.

Figure 5. OSLD reader - microSTARii (Landauer, France).

The manufacturers grow crystals, which are ground and made into different forms. During the manufacturing process of nano-dots (Landauer, France), the Al_2O_3:C crystals are crushed and sieved. The powder is layered on a polymer substrate and covered with a foil to make a tape. It results in a 0.3 mm thick dosimeter tape cut in pieces and embedded in light-tight plastic envelopes, resulting in a 4 mm diameter readout area. Even though before a tape is produced, the powder is mixed to be homogenous, the dosimeters have different sensitivities, and for accurate dosimetry, each one has to have an individual sensitivity correction factor determined before its use. During the reading process, the dosimeter is exposed to light. The light simulation can be continuous-wave, linearly-modulated, or pulsed optically stimulated luminescence. The advantage of the pulsed method is an improved signal-to-noise ratio by employing time-resolved measurements to discriminate between the luminescence and the stimulation light. The photomultiplier tube (PMT) is used to measure the luminescence signal. The optical simulation with the low-intensity light source allows for multiple readouts, as not all of the trapped charges are stimulated at once. A very short <1s pulse stimulates the luminescence so the dosimeter can be read multiple times without losing much signal. The dosimeters must be handled carefully and read reproducibly to achieve good reproducibility of readings [10-15].

The nanoDot dosimeter has a sensitive element of 4 mm diameter and 0.2 mm thickness, which is enclosed in a plastic light-tight case (10 mm ×10 mm × 2 mm). The sensitive material is aluminum oxide doped with carbon (Al_2O_3:C). Pulsed high-power light -emitting diodes (LED) are used to induce luminescence in the material. To ensure that the sensitive material of the nanoDots is not exposed to light, they are stored in light-tight containers. Each dosimeter is labeled with a unique serial number and a bar code. The microstrip reader allows the reading of one OSLD at a time, and the readout process is speedy, requiring only one minute to perform four readout measurements of a single dosimeter. The depletion of the signal on a dosimeter is observed with every successive re-readout. The whole system is very compact, requiring only a tiny space. The OSLDs can be reused after an optical annealing process. A light box was custom-made, and multiple lines of LEDs were installed on the top and bottom of the box to provide a uniform light intensity. A transparent glass drawer is in the middle for positioning OSLDs and ventilation for temperature control. Annealing for 60 minutes per 1 Gy dose is used; it reduces the accumulated signal to the background level and allows nanoDots to be reused [14-16].

The dose calculation from the OSLD system is based on a group of factors defined during the commissioning of a batch of OSLD. Factors include system sensitivity (SS), depletion (KD), an element correction factor (ECF), linearity (KL), and energy

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correction (KE) [16].

Radiophoto luminescence dosimeters (RPLDs)

The RPLDs are based on the radio-photoluminescence phenomenon. They are made of silver-activated phosphate glass containing silver ions. These ions capture the electrons and holes generated by ionizing radiation, creating luminescent centers that remain highly stable for years against room temperature and visible photoluminescence. An ultraviolet laser excites the centers, producing fluorescence proportional to the dose. This phenomenon is called radiophotoluminescence. The silver-activated phosphate glass, FD-7, is currently the most commonly used RPLD material. The elemental composition of the FD-7 glass is as follows: P:31.5, O: 51.2, Al: 6.1, Na: 11.0, Ag: 0.2 weight percent. When PO4 in glass is irradiated, it loses its electron and traps positive holes (hPO4). At the same time, Ag+ ions trap an electron released by PO4 and become Ag0. Similarly, hPO4 will merge with Ag+ to become Ag2+. Both Ag2+ and Ag0 function as stable luminescence centers. After excitation with 337.1 nm pulsed UV laser light, the electrons in Ag2+ and Ag0 excite to higher energy levels and emit 600-700 nm visible light when returning to their luminescence centers. An RPL dosimeter can be read repetitively without losing its signal as the laser pulsed method does not give electrons enough energy to escape from luminescence centers (only the annealing process at 400°C gives them enough energy so they return to the valence band). The excitation time duration is single microseconds. The main characteristics of glass detectors are excellent uniformity and not requiring individual detector sensitivity correction; Dose readings can be repeated multiple times; Dose readings are highly reproducible; Fading is negligible, and reliability is high [17-20].

Examples of commercially available RPLDs produced by Chiyoda Technol Corporation in Japan can be seen in figure 6.

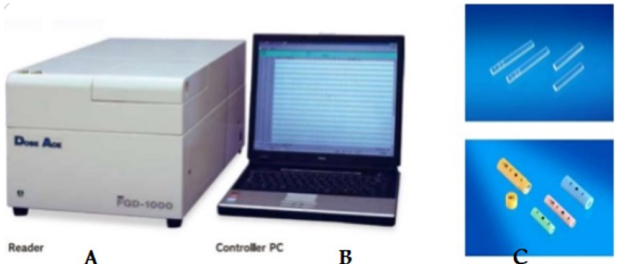

Figure 6. DoseAce dosimetry system using RPLDs. The general view of the Reader is on the left, and the RPLDs are on the right.

A Dose Ace system consisting of GD-302M glass rods and an FDG-1000 reader from Asahi Techno Glass Corporation (ATG) is used. The glass rods are made of silver-activated phosphate glass; they are 12 mm long and 1.5 mm in diameter, with an ID number engraved on one end. The sensitive area of a dosimeter is 6 mm long [17, 18]. RPLDs are encapsulated in custom-made watertight capsules. Each capsule has an ID number and a bar code. The sensitive area is also marked on the capsule to allow precise positioning (figure 7).

Figure 7. Waterproof capsules with an ID number and a barcode.

The FGD-1000 reader can read up to 20 glass rods in a session of 5 min (figure 8). After irradiation, the dosimeters are kept in a low-humidity storage cabinet for 24 h and are then preheated to 70°C to stabilize the luminescence centers.

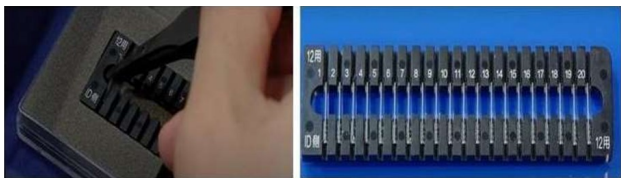

Figure 8. The FGD-1000 reader can read up to 20 glass rods in a session of 5 min.

RPLDs can be read several times as the readout process is not destructive. Depletion of the signal can be observed when a dosimeter is read repeatedly in quick succession, after which the signal returns to the initial value. Dosimeters can be reused after annealing (20 min at 400°C), eliminating luminescence centers. The absorbed dose is determined from the dosimeter readings using the dosimetry system calibration coefficient and some correction factors for dose-response non-linearity, energy, fading, and the holder [17-20].

Film dosimetry

The films have very high spatial resolution and are considered very attractive 2D dosimeters, particularly for measurements of steep dose gradients or highly modulated dose distributions typical for modern RT techniques. There are two main types of films: radiographic and radiochromic.

Radiographic films have been applied for 2-D dosimetry for a long time and are currently being replaced by radiochromic films, which do not need any chemical processing in a dark room. Radiographic films consist of grain emulsion (AgBr) layered on the base or substrate and covered with protective foil. The irradiation of the film causes Br ion to release the electron, which then converts Ag+ into Ag atoms. In that way, the latent image is created, which must be developed in a chemical process. The film's response depends on the processing conditions, including, for example, the temperature of the developer. The radiation effect on the film changes its light opacity, which is expressed as the ratio of the light intensity without the film and the light intensity transmitted through the film, which can be measured with the

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densitometer. Radiographic films have a limited range of linear dose-response; their response is energy-dependent and sensitive to low-energy photons [21].

Radiochromic film is a new type of film in radiotherapy dosimetry. The most commonly used is a Gafchromic™ film produced by Ashland Specialty Ingredients, Bridgewater, NJ, USA. Radiochromic films are designed to provide fast and highly accurate measurements for radiotherapy applications. Gafchromic™ RTQA2 films are intended for radiotherapy machine quality assurance, including, but not limited to, light field alignment tests, radiation field alignment tests, Star Shot tests, Picket Fence tests, Flatness and Symmetry tests, position verification for high dose rate brachytherapy. It is a colorless film with a near-tissue equivalent composition (9.0% hydrogen, 60.6% carbon, 11.2% nitrogen, and 19.2% oxygen) that develops a blue color upon radiation exposure and can be used in the dose range of 0.2 Gy – 10 Gy [22-25].

Radiochromic films are made of radiation-sensitive monomers incorporated into a gelatine layer and coated onto a polyester base. During radiation exposure, the polymerization of diacetylene molecules takes place, which causes polydiacetylene dye to be formed. The Gafchromic EBT3 self-developing dosimetry film has been developed specifically for applications in radiotherapy in the processor-less environment of the modern medical center in a dose range of 0.1 cGy – 10 Gy. The image is visible without any additional processing immediately after the irradiation (figure 9).

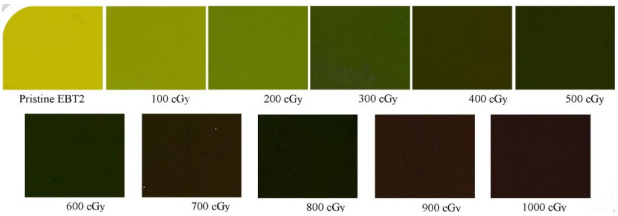

Figure 9. Example of irradiated Gafchromic films.

Since radiochromic film is grainless, it has a very high resolution. It can be used for dosimetry in high-dose gradient regions (e.g., measurements of dose distributions in stereotactic fields and in the vicinity of brachytherapy sources).

Dosimetry with radiochromic films has a few advantages over radiographic films, such as ease of use; elimination of the need for darkroom facilities, film cassettes, or film processing; dose rate independence; better energy characteristics (except for low energy X-rays of 25 kV or less); and insensitivity to ambient conditions (although excessive humidity should be avoided). Radiochromic film is a relative dosimeter. If proper care is taken with calibration and the environmental conditions, a precision better than 3% is achievable. Data on the various characteristics of radiochromic films (e.g., sensitivity, linearity, uniformity, reproducibility, and post-irradiation stability) are available in the literature.

Proper film handling is critical, as several items need to be taken care of carefully [22-25]. Timing between the irradiation and scanning has to be kept constant for a group of films, which will be analyzed together as the film continuously develops for several hours after irradiation. The disadvantage of Gafchromic films is that they darken with time, and the consistency of information stored on film is temperature-dependent.

The Gafchromic films require the preparation of a calibration curve covering fully the anticipated range of dose measurements. The scanning of the irradiated EBT3 films is performed with an EPSON 11000XL flat -bed scanner (EPSON, Japan) using the transmission mode, 150 dpi resolution, and 48-bit RGB color scale. The calibration films are irradiated with seven doses ranging from 0.5 to 6 Gy. The calibration films are irradiated within two weeks of a phantom's audit irradiation. The film's calibration curve and dose distributions are obtained using FilmQA Pro (Ashland, USA) software with the triple channel method [22].

DOSIMETRY ORGANIZATIONS

Dosimetry audit organized by the International Atomic Energy Agency (IAEA)

General

The IAEA and the WHO started the IAEA/WHO TLD postal dose audit program in 1969 [3-7]. The program aims to improve the accuracy and consistency of clinical dosimetry in radiotherapy hospitals worldwide. Since 1981, it has audited Secondary Standard Dosimetry Laboratories (SSDLs) to achieve consistency in basic dosimetry worldwide. Initially, the program was developed for Co-60 therapy units, but it also included audits of high-energy X-rays produced by clinical accelerators from 1991.

Thermoluminescence dosimeters (TLDs) are used as transfer dosimeters, and these are evaluated at the IAEA Dosimetry Laboratory. The most cost-effective method for performing external audits of beam calibrations is using thermoluminescence dosimeters (TLDs) [26-28].

For the radiotherapy centers from developing countries participating in the IAEA/WHO TLD postal dose audit program, it is practically the only opportunity to participate in an external audit program [6]. The program works so that thermoluminescence dosimeters (TLDs), consisting of encapsulated LiF, are sent to the participating center, where they will be irradiated to a specific dose. The TLDs are then returned to the IAEA Dosimetry Laboratory, located in Seibersdorf near Vienna, Austria, where they are read out, and the absorbed dose is evaluated from the TLD readings.

The maximum acceptable discrepancy between the dose stated by the center and the dose evaluated

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by the IAEA is 5 %. Should the discrepancy be larger, an additional audit is performed. If the second audit also gives a deviation larger than the limit, the center is offered assistance from the IAEA to resolve the problem. The acceptance limit for Secondary Standard Dosimetry Laboratories (SSDLs) is 3.5 %. The participant receives a data sheet to fill out. The provided information should include the method used for determining the absorbed dose, which facilitates an investigation in case of an unacceptable result. Generally, a beam at a participating center is checked biennially, except when results outside the acceptance limit have recently been encountered. In these cases, yearly checks are performed [29].

Dosimetry procedure

The procedure of the IAEA/WHO TLD postal dose audit program is shown in figure 10.

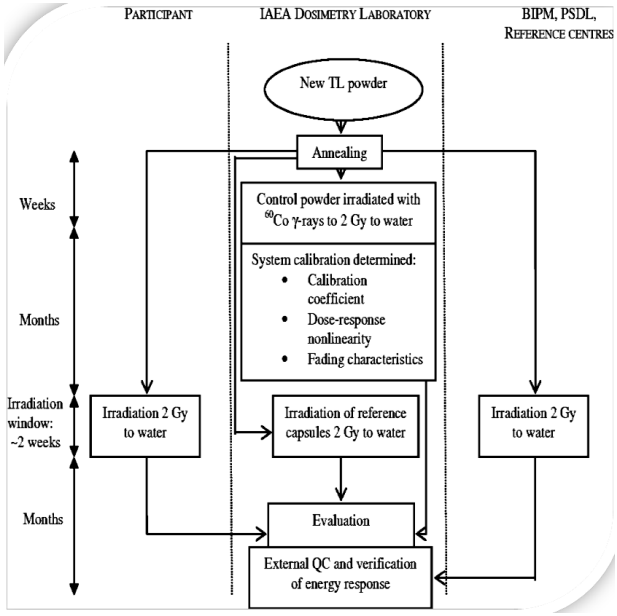

Figure 10. Procedures for the IAEA/WHO TLD postal dose audit program.

The participating radiotherapy center is asked to irradiate two TL dosimeters sequentially to a dose of 2 Gy to water. The irradiation occurs under the conditions of 10 cm depth in water, 10 cm x 10 cm field size, and the nominal source-to-surface distance (SSD) or source-to-axis distance (SAD) used clinically in the center. Participating SSDLs are asked to irradiate three TLDs under reference conditions. The dosimeter is placed in a plastic holder, which the IAEA provides during irradiation. The holder is shown in figure 11. The irradiation is requested to occur during a specific time frame (irradiation window), usually the month's second half. The calibration coefficient used in the dose evaluation is determined from the so-called reference capsules, which are irradiated at the IAEA within the same irradiation window as the participant's dosimeters since it is essential that the fading is about the same for both types of dosimeters.

In addition to the TLDs to be irradiated, one control capsule that has already been irradiated to 2 Gy at the IAEA is also sent to the center. This dosimeter detects possible environmental influences during the transport and storage of the TLDs.

As an external quality control, reference irradiations are performed in every irradiation window by the Bureau International des Poids et Mesures (BIPM) or by at least one Primary Standard Dosimetry Laboratory (PSDL) and by a reference center. Reference centers are leading hospitals in IAEA Member States. The primary level laboratories and reference centers provide the IAEA with irradiations with Co-60 gamma rays. The reference irradiations are used as an external verification of the accuracy of the dose determination by the IAEA, and those performed at reference centers are also used to verify the energy correction values. The system calibration, which includes the calibration coefficient, dose-response non-linearity, and fading characteristics, is determined for every annealed batch of LiF powder. Control powder is irradiated with 2 Gy at the IAEA and is used to follow the fluctuations of the reader [3-7, 28, 29].

Figure 11. The IAEA standard holder where the dosimeter is placed during irradiation at the participating center.

The IAEA dosimetry audit service today covers radiotherapy centers in East Europe, Africa, and South America, as shown in figure 12 [29].

Figure 12. Geographical region coverage by the dosimetry audit organized by IAEA [29].

RESULTS

Results of TLD irradiations performed during 1969-2003 in Eastern and South-Eastern Europe and Latin America have previously been discussed elsewhere [4- 5], as well as the results of TLD

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irradiations performed worldwide during 1998-2001 [3]. Hospitals that regularly participate in the program obtain better results than those participating for the first time. Analysis of results from recent years shows that the percentage of centers participating for the first time and having results within the acceptance limit is 78 %. In comparison, 90 % of the centers participating yearly have acceptable results [4].

Over the 50 years, the IAEA/WHO postal dose audit service has undergone several scientific reviews, technical improvements, and various developments that have led to better organization and efficiency [30].

2,364 radiation therapy centers in 136 countries have been audited in the five decades. 4427 radiation therapy machines generating 5790 photon beams were tested, and 13756 results were obtained. On average, 86% of audit results are within±5% tolerance [31].

Figure 13 shows the distribution of audit results presented as Dm/Ds ratios of the IAEA measured dose (Dm) and the dose indicated by the inspected center (Ds) for the period 1969-2018.

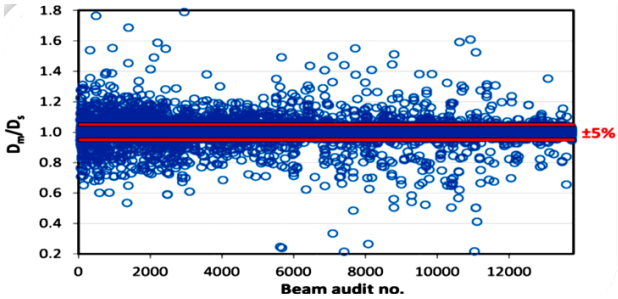

Figure 13. Results of a dosimetry audit conducted by the IAEA/WHO in 1969-2018. 13,756 audits of photon beams generated by 4,427 radiotherapy devices in 2,364 radiotherapy centers from 136 IAEA member states [31].

In 2017, the IAEA Dosimetry Laboratory upgraded its laboratory equipment with a new Dose Ace system, which uses glass dosimeters [32]. Since June 2021, the IAEA/WHO postal audits service has been expanded to include electron beams. The methodology is developed in the IAEA Dosimetry Laboratory, including using a laboratory-made holder system to position dosimeters at the reference depth, measuring all relevant correction factors for determining absorbed dose, and multi-center testing of the methodology. The new audit service is available for radiotherapy departments in the Member States [33].

Dosimetry audit organized by imaging and radiation oncology core (IROC - H) Houston QA Center

General

Imaging and Radiation Oncology Core (IROC) Quality Assurance Center is based in Houston, Texas, USA, and is now known as (IROC-H). It has the most extensive dosimetry program in the world. Dosimetry audits include all radiation therapy centers in the United States. The IROC – H/Radiological Physics Center (RPC at that time) was established as a resource in radiation dosimetry and physics for cooperative clinical trial groups, and all radiotherapy facilities that deliver radiation treatments to patients entered into cooperative group protocols in 1968 [34].

The IROC–H has functioned continuously for more than 50 years to assure National Cancer Institutions (NCI) and the cooperative groups that institutions participating in multi-institutional trials can be expected to deliver radiation treatments that are clinically comparable to those offered by other institutions in the cooperative groups. To accomplish this, the RPC monitors the machine output, the dosimetry data utilized by the institutions, the calculation algorithms used for treatment planning, and the institutions' quality control procedures. The monitoring methods include an on-site dosimetry review by an RPC physicist and various remote audit tools [34].

The IROC Houston QA Center's contributions to quality assurance of radiotherapy treatment of patients entered into cooperative clinical trials include three major areas:

On-Site Audit: "On-site dosimetry reviews" are performed to help institutions resolve problems and verify the validity of important mechanical and radiation parameters used by the institution for each therapy unit. Data collected are used:

- In the retrospective evaluation of patient charts from those sites visited.
- In generating standard data used to evaluate patient charts in general.

In the resolution of dosimetry problems at the institution.

Off-Site Audit: Since not all participant facilities can be visited routinely, several "off-site dosimetry review" auditing techniques have been developed. These include:

- A mailable TLD program to verify machine output periodically.
- Comparison of the institution's dosimetry data with IROC Houston's "Standard dosimetry" data to identify potential problems with the data used for patient dose calculations.
- Evaluation of reference/or actual patient calculations to verify treatment planning algorithms.
- Review of the institution's written QA procedures and records.

Mailed anthropomorphic phantoms to verify tumor dose delivery for special treatment techniques such as IMRT, stereotactic radiosurgery, etc.

Collaboration: Close collaboration with other quality assurance offices and feedback on instructive findings for the radiotherapy community while maintaining the anonymity of participating institutions.

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•Credentialing of institutions for participation in specific protocols.

Retrospective review of treatment records for patients entered into cooperative clinical trials.

The IROC Houston continuously modifies its techniques to reflect new protocols and changes in practice at participating institutions. It also continues to research dosimetry questions that arise from multiple institutions using various therapy equipment to deliver clinically comparable treatments. The IROC Houston is a radiation dosimetry and physics resource for the medical physicist community and all nine cooperative groups [34 - 45].

Figure 14 shows the geographical region covered by the dosimetry audit services of IROC—H, which includes all radiotherapy centers in the USA and some countries in South America, Africa, and Australia.

Figure 14. Geographical region coverage by the dosimetry audit organized by IROC-H [29].

Dosimetry procedure

IROC Houston commissions a new batch of TLD powder each year for the mailed TLD program. /See Fig. 15/ Each batch of powder yields nearly 100,000 capsules. The commissioning process includes verifying the fading correction, non-linearity correction, energy correction, and dose-response (sensitivity). The TLD dose is determined from dosimeter readings using the following factors as follows:

S - System sensitivity determined each session, V/mg - Sample response per unit mass, KF - Fading correction (range 5-160 days), KL - Non-linearity correction (doses 50 - 600 cGy), KE - Energy correction (photons: 60Co - 25 MV, electrons: 5 - 25 MeV), KISQ - Inverse square correction, F - Peak scatter factor for dose to complete phantom, DDF - Depth dose factor, KDECAY - Decay correction for 60Co measurements.

A TLD system is used to periodically verify that an institution is within acceptable limits in beam output for photons and electrons, identify institutions with potential problems, and flag them for additional review. The activities of the TLD dosimetry program can be described as follows: Monitors beam output for photon beams (60Co - 25 MV) and depth dose data for electrons (5 - 25 MeV). The acceptance criteria for absorbed dose TLD/Inst = ± 5 % and electron Percent Depth Dose (PDD) = ± 5 mm [36-37].

Figure 15. The remote dosimetry audit with thermoluminescent dosimeters-TLDs in IROC-Houston [34].

IROC Houston migrated to OSL dosimetry for the remote verification of standard calibration of radiotherapy units on June 1st, 2010 (figure 16) [34].

The OSL dosimeters are irradiated with a dose of only 100 cGy. They are reusable, and unique organization is applied to quick turnaround in the irradiation and return of the dosimeters so that they can be used again. IROC-H has performed extensive tests and commissioning of the dosimetry system and is highly confident in its performance. The OSL dosimeters are used to monitor beam output and depth dose data for electrons (5 - 25 MeV) and beam output for photons (60Co - 25 MV). The acceptance criteria are followed: Absorbed dose OSL/Inst =5 %; Electron PDD=3 mm (beam energy ≤16 MeV) and Electron PDD =4 mm (beam energy ≥16 MeV) [40-43].

The OSL technology provides several benefits to improve the quality and efficiency of the IROC-H dosimetry audits. They are: Simpler readout procedures; Optical technology means that no heating is required; A laser illuminates dosimeters to stimulate the emission of light that is proportional to the absorbed dose; The readout period of only seven seconds, rather than roughly 45 seconds with TLD; IROC Houston acquires several readings from each dosimeter, and uses two dosimeters at each measurement location; Acquisition of the signal from the dosimeters at each location thus requires approximately 30 seconds, rather than the 6 minutes needed for TLD; Dosimeters are environmentally stable; Readout is nondestructive; Multiple readings of each dosimeter are possible; Repeat readings can be made, even weeks or months later; Minimal fading of signal and minimal energy dependence [40-45].

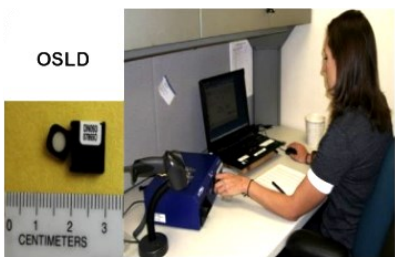

Figure 16. The remote dosimetry audit with OSLD nanoDot (optically stimulated luminescent dosimeters) in IROC-Houston [34].

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Over the past two years, IROC Houston has been in the process of acceptance testing, commissioning, and designing an OSL system for the mailed audit activities. This has included accepting and commissioning readers and dosimeter characteristics, designing procedures for data taking, dose calculation, data processing, and quality assurance.

Results

The dosimetry audit program is constantly growing. In 2015, over 2,100 institutions were audited, and more than 22,600 beams were inspected, making the program the largest in the world. Over 16,000 results were obtained with TLD dosimetry and more than 4,200 with OSLD dosimetry. The mean of the dose ratio Dmeas/Dstat at the checkpoint was 1.000 ± 1.9% for TLD and 0.999±1.7% for OSLD. The results of more than 20,000 dose measurements under reference conditions are shown in the figure 17. Of more than 20,000 measurements, only 2.4% were outside of the 5% tolerance established by IROC-Houston [34].

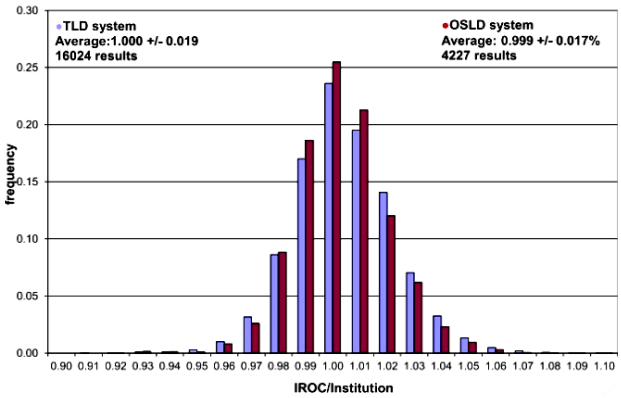

Figure 17. 20,000 Remote Dosimetry Audit results at IROC-Houston with thermoluminescent dosimeters-TLDs and OSLD nanoDot-optically stimulated luminescent dosimeters [34].

The IROC-H QA Center monitors 2,214 institutions, with over 4,400 therapy machines participating in cooperative group clinical trials sponsored by the NCI, other National Institute of Health trials, EORTC trials, and pharmaceutical company trials. These institutions are located primarily in the USA and Canada and include 365 participants from 52 countries [45].

Dosimetry audit organized by EQUAL ESTRO Laboratory

General

The EqualEstro laboratory was established in 1998 to perform external audits of radiotherapy beams for all European centers. The first postal dosimetry audit was organized in that year. The mission of EqualEstro Laboratory is to bring excellence in patient care by providing customers with a full range of quality control services and products within the specific field of radiation oncology.

In 2002, the laboratory launched a new dosimetry audit, allowing verification of dosimetry quantities and parameters characterizing complex radiotherapy fields modified by a multi-leaf collimator. A dosimetry audit was also introduced to control physical quantities characterizing brachytherapy. Until the end of 2003, it was funded by EC projects. In 2004, the EqualEstro laboratory was accredited [46-50]. Since the beginning of the activities, 46% of the French radiotherapy centers and 55% of the European radiotherapy centers have participated in the EqualEstro Quality Control program [46].

Figure 18 shows the region covered by the dosimetry audit service offered by the Equal Estro laboratory.

Figure 18. The region covered by the dosimetry audit service offered by EQUALESTRO Laboratory [29].

Procedure

All audit services provided by EqualEstro are based on remote procedures, using TLDs or TLDs and films. The TLDs are used for point-dose measurements, whereas films are employed for 2D dose distribution measurements. The TLDs provided by Equal are powder-type dosimeters using TLD-700® lithium fluoride (LiF) encapsulated in polyethylene tubes. The active volume of these dosimeters is 20 mm in length and 3 mm in diameter. The reading is performed with an automated PCL-3 reader from Fimel (France). GafchromicTM EBT3 (Ashland Specialty Ingredients, Bridgewater, NJ, USA) films are used for the film measurements. The readout of films is performed using a commercial flatbed scanner, Epson® Expression® 10000XL. Film images are compared to TPS plans using a commercial IMRT QA software, OmniPro ImRT (IBA Dosimetry). Dosimetry audit based on film dosimetry assesses the 2D dose distribution. For this purpose, a water-equivalent geometric phantom is used with inhomogeneities such as lung and bone tissues. The phantom allows the positioning of films in the axial, coronal, and sagittal planes up to 16 cm x 16 cm in size [47-54] (figure 19).

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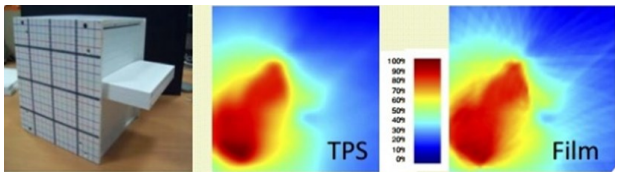

Figure 19. Film dosimetry in the Equal Estro laboratory used for remote dosimetry audit purposes [46].

Over the past 10 years, with other national and international audit organizations, the EqualEstro laboratory has developed and provided new methodologies for dosimetry audits in modern radiotherapy, including new dose delivery techniques such as IMRT, VMAT, Tomotherapy, and CyberKnife [51-55].

In the period 2014 - 2018, an "end-to-end" dosimetry audit was developed to check tomotherapy equipment with a specially designed phantom [46, 51-55]. The audited center receives the phantom and the CT images needed to prepare the radiotherapy plan. Planning and irradiation of the phantom must be performed at the audited center according to the protocols used. The only limitation imposed by the EqualEstro laboratory is that the maximum prescribed dose be no higher than 8 Gy. A total of 43 dosimetry audits were carried out, with some radiotherapy equipment being checked more than once.

Results

More than 9000 therapy beams, photons, and electrons were tested using a remote TLD method within a mandatory audit program of beam calibration parameters [53]. The reference beam output tests, using TLD measurements, show results in the acceptable range for all tested units. Moreover, for almost 90% of the tested units, the measured dose deviation is within 1%. Only one unit showed a deviation from 3 to 5%.

For all the French beams checks, the following results have been observed: for the photon beams, the results show that about 1% of the measured doses in the reference conditions on the axis have been detected outside the tolerance level (deviation between the measured dose and the stated dose > +/- 5%) after a first or a second check. For points checked in photon beams with wedge filter, 2.5% of the beams checked show a deviation > +/- 5% after a first or a second check. For the 180 electron beams checked, 5% of the measured doses in the reference conditions have been found outside the tolerance level (> +/- 5%). These results clearly show the importance of quality control in radiotherapy in the frame of an external audit [54].

The results of the film dosimetry audit are also excellent, as in 98% of cases, the requirements of the gamma criterion for distance and dose/γ index, 2D global gamma passing rates with a gamma criterion of 5%/3 mm are met.

The 2D film images are compared to the radiotherapy plans by the planning systems, taking into account the accepted eligibility criteria as follows:

- 2D film images - Dose deviation must be less than 10% for at least 90% of the film surface.

The gamma test for dosimetry comparison should be 5%/3 mm as the result of 5% of the dose value should be higher than 90% for the audited centers.

Film measurements have shown acceptable results for all tests performed. For more than 70% of the radiotherapy plans audited, the gamma test criteria were higher than 95%.

EqualEstro is working with more than 300 radiotherapy centers worldwide overcoming cultural, language and methodological barriers. The selection of centers is a crucial efficiency factor. The number of participating centers is increasing rapidly, ensuring a higher rate of patient inclusion. An international network of experts is involved in each study. These experts are helping to design radiotherapy protocols. They are auditing the centers. They review patient treatment plans before treatment delivery. EqualEstro is the only QA provider based in Europe that offers this comprehensive external audit service and the only QA company accredited by the French government to perform the yearly external audits required by law [47, 54].

DISCUSSION

The dosimetry audit is a highly specialized activity that requires special knowledge, skills, efforts, and time to organize and conduct by the requirements for good dosimetry practice in all radiotherapy centers worldwide.

This is a challenge for the professional community of medical physicists when 8,500 radiotherapy centers in 150 countries worldwide are registered in the IAEA Directory of Radiotherapy Centers (DIRAC), and they operate approximately 20,000 radiotherapy machines to treat cancer patients [56].

Some high-income countries such as North America, Japan, Australia, and several European countries (e.g., Belgium, Czech Republic, Finland, France, Greece, Germany, Netherlands, Norway, Poland, Slovakia, Switzerland, and the UK) have good dosimetry audit coverage. Only 2/3 of radiotherapy centers in the world received some level of audit [57].

This indicates a need to increase the availability of audits worldwide. According to the IAEA dosimetry audit network (DAN) data in 2017, 45 organizations in 39 countries confirmed they operate dosimetry audit services for radiotherapy. Most of the audits are conducted on the national level [29].

The largest dosimetry organizations in the world, through their large-scale activity in the field of dosimetry in reference conditions, have proven

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undoubtedly that the dosimetry audit is a target that focuses on trends of safety, efficacy, and control of the radiotherapy process as a challenge and necessity for the implementation of the quality assurance program for radiotherapy in general and clinical radiation dosimetry in particular.

Despite the long-term and large-scale activities in the field of reference dosimetry, some differences are observed in the frequency and number of beams to be analyzed. While IROC-H asks for every machine and energy yearly, the IAEA asks every two years. IAEA uses as a detector RPLDs while IROC uses OSLD/TLDs and ESTRO – EQUAL TLDs. In addition, the acceptable limits differ, with IAEA and EQUAL-ESTRO requiring results within 5% while IROC asks for 3% [58].

Radiotherapy technologies have significantly improved recently, reaching high complexity and sophistication. The rapidly increasing use of newer techniques, including hadron therapy, is expected to represent an added value for the patient regarding clinical outcomes. However, it places new demands on quality assurance programs, as well as new attitudes and approaches for patient safety [58].

However, the known benefits come along with an increased potential for errors. The complexity of most associated procedures, including basic dosimetry, planning process, and treatment delivery, is also increased [59-61]. Complexity has been described in many publications as "the frequency and amplitude of fluctuations in the intensity distribution of a beam" [61]. Many monitor units (MU) and small, narrow, off-axis, and/or irregularly shaped apertures characterize a high complexity level [62]. As reported, the degree of complexity of a beam/plan can significantly compromise treatment deliverability due to multileaf collimator (MLC) positioning accuracy, linear accelerator (linac) performance, and/or limitations in dose calculation [63, 64].

In the last two decades, intensity-modulated radiation therapy (IMRT), including volumetric-modulated arc therapy (VMAT), has become extensively used in daily clinical practice. Therefore, new audit methodologies must be developed to follow the advancements in radiotherapy. The audits should start with simple checks of the beam output in the reference conditions and grow in complexity by verifying more advanced dosimetry parameters until the critical steps in the patient treatment chain are validated through an end-to-end test. The audits should start with a simple check of the beam output in the reference conditions and grow in complexity, verifying more advanced dosimetry parameters until they reach the critical steps in the patient treatment chain. This new type of dosimetry audit is called an end-to-end audit and independently verifies the entire IMRT/VMAT treatment chain, covering all steps from imaging to dose delivery.

The largest dosimetry organizations responded to this challenge by offering an end-to-end audit, realizing that the traditional dosimetry audit of beam output in reference conditions has limited capabilities. The IAEA 'end-to-end' audit methodology was first developed for 3-D conformal radiotherapy (CRT) in 2008 [65]. It reviewed the dosimetry, treatment planning, and radiotherapy delivery processes using the 'end-to-end' approach, i.e., following the pathway similar to that of the patient through imaging, treatment planning, and dose delivery Similarly to the 3 D CRT end-to-end audit, the IAEA developed new audit procedures for end-to-end auditing of intensity-modulated radiotherapy (IMRT) and volumetric arc therapy (VMAT) using on-site visits. The objective is to review the medical physics aspects of the overall clinical IMRT performance and to provide feedback to the participating radiotherapy centers regarding the quality of a typical clinical head and neck IMRT/ VMAT treatment to ensure the optimal and safe usage of these techniques.

The methodology simulated the essential parts of the external beam IMRT/VMAT radiotherapy workflow, from patient data acquisition to treatment planning and dose delivery. This audit uses an anthropomorphic phantom, "Shoulders, Head and Neck, End-to-end" (SHANE, developed by CIRS), to be close to a realistic patient procedure. The audit package includes the instructions and data reporting forms, a SHANE phantom, and a set of contours representing the target volumes and organs at risk [66, 67] (figure 20).

Figure 20. Anthropomorphic phantom "Shoulders, Head and Neck, End-to-end" (SHANE, developed by CIRS).

The IROC–H QA Center implemented a remote program for clinical trials credentialing H&N IMRT treatments using a semi-anthropomorphic phantom in 2001 [68] (figure 21).

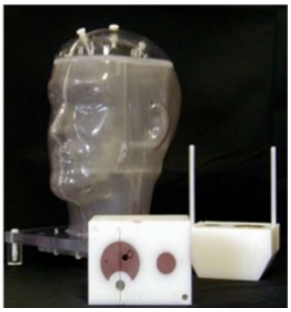

Figure 21. The IROC-H's H&N phantom.

This is the most common phantom shipped to institutions for an "end-to-end" dosimetry audit of the IMRT technique, having been sent over 2,400 times since 2001. In addition to the H&N phantom,

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the RPC/IROC-H also has pelvic, thorax, liver, spine, and brain phantoms for photon and proton radiation therapy. Significant improvements in the results have been achieved over the years. However, about 10% of the irradiations still fail to meet the tolerances of ±7% dose difference for point dose measurement with thermoluminescent dosimeters (TLD) and 85% global gamma analysis (7% dose difference/4 mm distance-to agreement) for the film [67].

The audit methodology comprises the dosimetry verification of an H&N IMRT plan created by each participating institution and a set of tests to check small-field dosimetry, MLC performance, and machine beam output [66-68]. In 2014–2018, an "end–to–end" EQUAL-ESTRO Laboratory developed a dosimetry audit to verify tomotherapy facilities with a specially designed phantom shown in Figure 22 with tissue inhomogeneities (lung, bones, and cavities) [51-54].

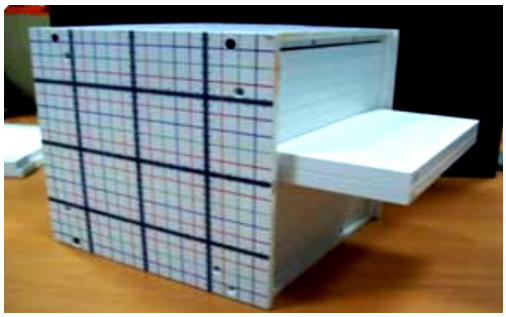

Figure 22. The EQUAL-ESTRO phantom.

A few dosimetry audits of SBRT and SRS treatments, which are complex and high-risk techniques, have already been set up [68, 69]. The methodology included checking the accuracy of small field output factors (OFs) calculated using TPS and testing the agreement between the TPS calculated and the diameters or the measured lateral small field profiles. The methodology was developed and tested for field sizes of 4 cm×4 cm, 2 cm×2 cm, and 1 cm×1 cm, circular fields of corresponding nearest achievable field sizes. It turned out that the dosimetry of small radiation fields is a real challenge these days. The largest dosimetry organizations have successively developed a methodology for dosimetry audits of small fields, but they are not organized on a large scale [70-72]. Extending the audit scope is especially important for the same types of machines, such as CyberKnife, GammaKnife, and TomoTherapy, which have specific characteristics that should be considered when performing an audit. IROC has prepared the tools to conduct audits to verify the output of machines such as CyberKnife, TomoTherapy, and GammaKnife [73, 74], as well as EQUAL-ESTRO Laboratory [53].

Finally, should be mentioned that a few novel auditing methods include phantom-less methods such as analyzing EPID data [75], log files [76, 77-79], and virtual EPID standard phantom audit (VESPA), which is tested by Miri *et al.* [80]. Still, they are not yet offered on a large scale.

CONCLUSION

The Largest Dosimetry Organizations reported extending their services to an inter-continental level where annually, the IAEA delivers audits to radiotherapy centers in 60–70 countries, IROC-Houston to about 60 countries, and EQUAL ESTRO to about 40 countries [29, 34, 46]. From the excellent work of the largest dosimetry organizations in reference dosimetry audits to the end-to-end test, which is very useful for identifying discrepancies between the calculated and delivered doses during radiation therapy [81], there is no doubt that the quality of radiotherapy has improved over recent decades, and the dosimetry audit has played a leading role.

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***Author contributions*:** All authors from the Sofia Medical University are equally involved in literature search, data synthesis, manuscript writing, critical editing, and illustrated by examples and images. Katia M. Sergieva, Lubomir L. Traikov and Valeria H. Hadzhiyska are equally responsible for the analysis, preparation and presentation of this manuscript. Katia M. Sergieva is responsible for revised manuscript.

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