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Review paper

Dosimetry procedure to verify dose in High Dose Rate (HDR) brachytherapy treatment of cancer patients: A systematic review

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ABSTRACT

High dose rate (HDR) brachytherapy is a widely accepted cancer treatment method which provides high cure rates. In a HDR brachytherapy treatment, high radiation doses are delivered to the tumor area by placing the radioactive sources in the close proximity to the region of interest. The brachytherapy dose delivery follows the inverse square law with rapid dose fall of leading to minimal damage to the surrounding normal tissue. The safe direct delivery of the radiation dose to the tumour leads to good treatment outcomes comparable to other modalities of treatment. Hence, it is crucial to maintain a sharp drop in the radiation dose distribution within very short distances. Treatment planning system (TPS) which is controlled by a computer algorithm plays a significant role in calculating the optimum doses to the tumour area during a typical HDR brachytherapy treatment. However, the optimum dose calculated by the TPS must be verified by using an independent testing method in order to eliminate under/over irradiation of the tumor region and as quality assurance. In general, two types of independent dose verification methods(experimental and computational) are used to crosscheck the doses calculated by TPS. This systematic review aims to summarize the studies done in the past ten years on HDR brachytherapy treatment planning verification and to analyze the reliability and limitations.

1. Introduction

Cancer has become a leading cause of death worldwide [1]. According to the World Health Organization (WHO), millions of people are diagnosed with cancer each year, and more than half of these patients eventually succumb to the disease [2]. Brachytherapy is commonly used in the curative treatment of cancers, in particular for gynaecological (GYN) cancers such as cervical, endometrial, vaginal and vulval cancers in females and for prostate cancer in males [3]. Further, brachytherapy has been used less frequently in the curative treatment of breast, sarcoma and head & neck cancers [4]. Additionally, brachytherapy offers good palliation for oesophageal, bronchial and recurrent rectal neoplasms [5]. Compared with external beam radiation therapy, brachytherapy can deliver an ablative radiation dose directly to the affected tissue over a short period of time with the benefit of a steep dose fall-off, potentially sparing the neighbouring organs at risk (OAR) [4,6,7]. Based on the dose rate of the radiation delivery, brachytherapy has been categorized into High Dose Rate (HDR), Low Dose Rate (LDR), Pulsed Dose Rate (PDR) and Medium Dose Rate (MDR) brachytherapy. [3]. According to the definition of the International Commission on Radiation Units and Measurements (ICRU), if the numerical value of the dose rate at the dose specification points is greater than 12 Gy/h it is classified as HDR, and if the dose rate is in between 0.4 Gy/h and 2 Gy/h it is classified as LDR. Moreover, PDR uses stronger radiation sources than those employed in LDR brachytherapy and provides a series of short 10 to 30 min long exposures every hour. MDR delivers a dose rate of 2–12 Gy/h for the treatment [8]. This review article focuses on HDR brachytherapy and its dose verification.

Brachytherapy sources commonly emit photons and beta radiation. The neutron emitting sources are also used in a few specialized situations [9]. ^{60}Co, ^{137}Cs, ^{192}Ir, ^{125}I, ^{103}Pd and ^{90}Sr/^{90}Y are some commonly used brachytherapy sources. When selecting the appropriate radiation source for treatment, one should be mindful of the source strength, energy and the type of radiation emitted. In the beginning, ^{226}Ra and ^{222}Rn

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were commonly used in brachytherapy procedures, but abandoned due to radiation safety concerns [10].

Brachytherapy treatment planning and delivery involve a series of events. The calculation of the dose distribution to the target is one of the vital steps in the process. The treatment planning (TP) has been developed from basic lookup tables and computer-based dose calculation algorithms. The current approach to brachytherapy TP is based on the American Association of Physicists in Medicine (AAPM) task group No. 43 (TG-43) formalism [11,12]. Additionally, standard frameworks have been set on general guidance on quality assurance (QA) and quality control (QC) for clinical TPS by international bodies such as International Atomic Energy Agency (IAEA)-IAEA TRS 430 and European Society for Radiotherapy and Oncology (ESTRO) [13]. The general recommendation is that each component of the system is tested with autonomous and standard strategies. In each clinical use of brachytherapy, TPS should be verified using an independent and less error prone system [3]. An end-to-end calculation can validate more complex plans in the treatment with the appropriate patient and treatment-specific data.

AAPM TG-43 formalism has been developed with the assumption that the medium is uniform and it consists of water. TPS employs AAPM TG-43 formalism in estimating the planned dose. However, the effects of tissue heterogeneity, applicator and inter-source are considered as negligible in TPS calculations [14]. In response to the effect of these shortcomings, Model-based dose calculation algorithms (MBDCAs) were introduced and they are capable of providing more accurate dose distribution in the brachytherapy treatment [15]. Moreover, advanced formalisms such as AAPM TG-186 and MC based methods have been developed to incorporate the effects arising from the aforementioned factors in the planned dose calculation [16]. AAPM TG-186 formalism provides guidelines for clinical implementation of modern planning algorithms in brachytherapy. MBDCAs use Monte Carlo (MC) codes, which offer high accuracy for dose calculations in verification studies [17]. Regardless of the formalism being used in TP, dose verification using an independent method is vital to ensure QA and QC procedures. Dose verification is critical in the treatment procedure as it helps to minimize errors that lead to efficient treatment and to minimize side effects to the patient. Experimental methods, including various radiation detectors in solid/liquid phantoms, have been traditionally used as independent methods to validate the accuracy of the estimated dose of TPS [18]. In addition, the use of the MC method has expanded over the last decades to serve the same purpose [19].

The primary goal of this literature review is to evaluate the techniques in HDR brachytherapy dose verification over the last ten years. In addition, it is aimed to provide an overview of developments regarding the application of models for HDR dose optimization. The article is organized in the following way. The screening process of journal articles and the selection criteria are mentioned in Materials and Methods section. Literature survey related to the dosimetry verification procedure in HDR brachytherapy treatment is presented in the review section under two main categories: experimental studies and computational studies. Key points and the overview of the review article, along with the concluding remarks, are mentioned in the discussion and conclusion.

2. Materials and Methods

A literature review was conducted based on radiation dose distribution and dose verification studies in brachytherapy treatment during last ten years. The literature review has been done under two main streams: experimental dose verification methods and computational dose verification methods. The survey strategy adopted for this review was to seek comprehensive literature on various brachytherapy dose verification studies done in the past decade. Popular databases such as MEDLINE, PubMed, SCOPUS and Google scholar were used to carry out this systematic literature search. The keywords applied were “Brachytherapy dose”, “Brachytherapy dosimetry studies”, “Brachytherapy treatment planning system (TPS)”, “Brachytherapy dose verification, Monte-Carlo (MC)” methods, “tissue equivalent phantom”. The list of terms and keywords are included in Table 1. During the literature survey, 1285 related journal articles were identified: 656 from MEDLINE, 342 from PubMed, 254 from SCOPUS and 33 from Google Scholar. Out of 1285 articles, 974 were removed due to duplication, and another 246 were removed after the initial screening based on titles and abstracts. Further, 22 were excluded from the remaining 65 articles, as they focused on brachytherapy source designing/modelling methods, LDR brachytherapy studies and patient related studies. The remaining 43 articles were analyzed and classified according to experimental studies and computational studies. Articles related to experimental studies were further categorized under different radiation dosimeters used in the verification method. Fig. 1 illustrates the flow chart of the literature review process in accordance with the “Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)” guideline [20,21].

3. Review

3.1. Experimental studies

The experimental studies of dose verification in brachytherapy are grouped under different dose verification systems used in the studies conducted over the last 10 years. All these studies describe the accuracy of dose delivery against the planned dose distribution during the brachytherapy treatment. Verification of TPS is traditionally performed using solid, or liquid phantoms [14]. The experimental studies highly depend on the phantom design, phantom material and the type of radiation dosimeters. Radiochromic film, ionization chamber IC and thermoluminescence dosimeter TLD are standard detectors that are used to measure the dose around the target area in phantoms, while gel dosimetry is a new advancement in dose verification methods [22].

3.1.1. Verification using Radiochromic films

Film dosimetry has been developed as a tool for radiotherapy treatment verification and QA over the past few decades [23]. Film dosimetry provides two dimensional (2D) dose distribution for treatment verification in brachytherapy. Advantages of film dosimetry can be identified as high spatial resolution, ability to design to the shape of the experimental geometry, weak energy dependence in a broad range of beam qualities, and tissue equivalence [24–27]. When radiometric films are exposed to radiation, the colour is changed as a result of a polymerization process induced by ionizing radiation. The increase in color of the film is usually measured with a spectrophotometer or a densitometer. These measurements are expressed in terms of the increase in absorbance or commonly known as optical density. The difference in ODs of the film after and before irradiation is measured [23]. The developed films are processed using a scanner and analysed by custom software in which image pixel values can be converted to the radiation dose [28]. As radiochromic film is a relative dosimeter, calibration curves are used to convert the response of the radiochromic film into absolute dose [27]. In order to achieve accurate dose calculation, the environmental conditions should be taken into consideration [29,22]. Many experimental studies evaluated the efficiency of radiochromic films in brachytherapy dose verification [30,31]. Brown et al. [32] showed that the weak energy dependence of EBT3 film makes it a suitable dosimeter in ^{192}Ir based brachytherapy studies. The techniques of improving the accuracy of EBT3 film dosimetry was discussed in

Table 1
Terms and Key-words used for combined search strategy.

Brachytherapy	Phantom studies	TLD dosimetry
Treatment verification	Tissue equivalent phantom	Gel phantom
Dose verification	Heterogeneous phantom	
MatriXX	Monte-Carlo	

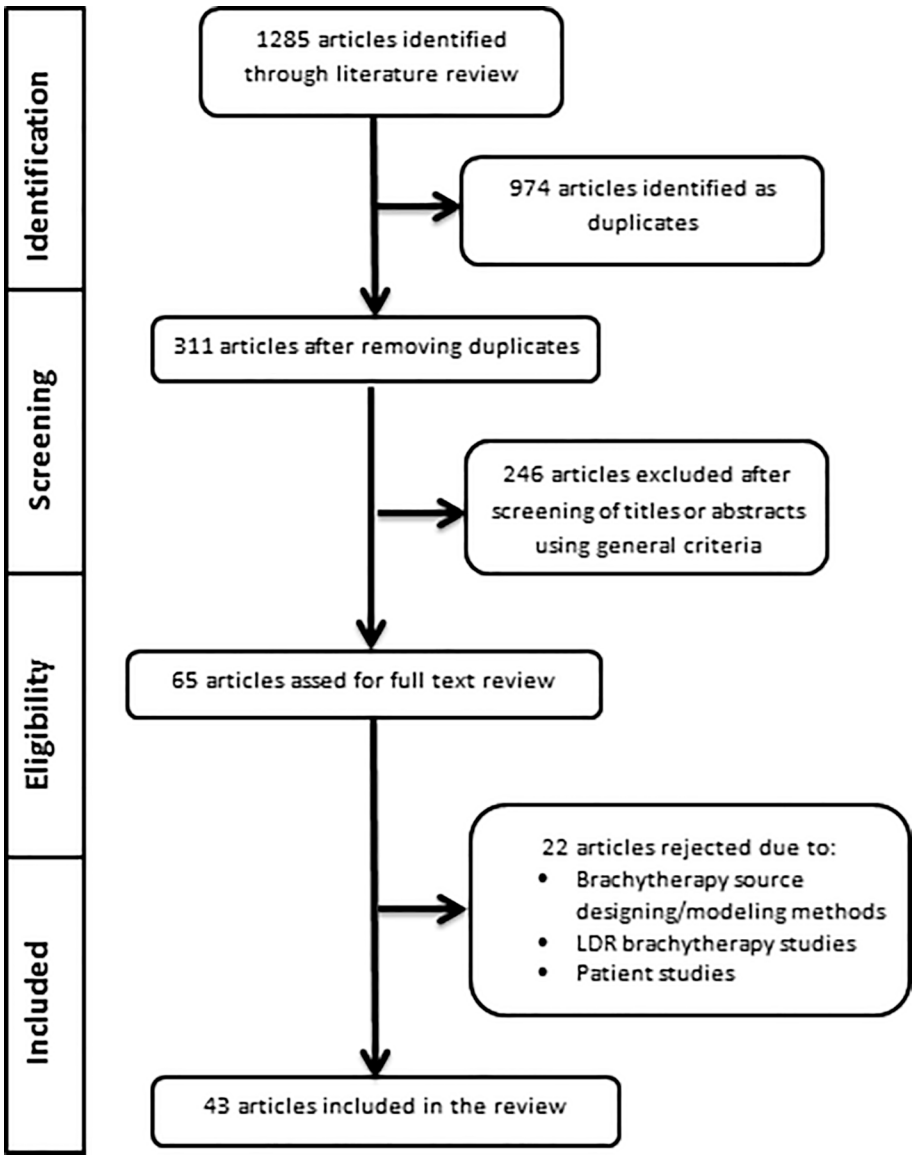

Fig. 1. Flow chart of the literature review process according to the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)" guideline.

Palmer et al. [33] while in Jeang et al. [34] study, the clinical applicability of 2D in vivo rectal dosimetry using the endorectal balloon (ERB) with EBT3 films for HDR brachytherapy was studied.

Many novel dosimetric systems with GafChromic films were developed to study the dose distribution in brachytherapy treatment over the past years[24,29,35,28]. Gholami et al. [24] has used film dosimetry for the dose verification of GYN brachytherapy treatment. The measured dose distributions were found to be in good agreement with the TPS isodose lines both numerically and spatially. However, the study confirmed that the dosimetry system was only able to measure differences of greater than ±6%. Palmer et al. [29] conducted a study with the purpose of developing a method for the dosimetric QC procedure of HDR brachytherapy treatment using Gafchromic EBT3 film. Multichannel dosimetric method has been employed in the analysis of the study which can remove many of the common disturbances usually present in radiochromic films. The result of the study has shown that EBT3 film can be effectively used as a dosimetric system in measuring dose distribution during brachytherapy treatment.

Asgharizadeh et al. [35] designed an EBT3 Gafchromic film based phantom model for patient-specific QA of HDR rectal cancer brachytherapy treatment plans. This dosimetry system showed higher dose homogeneity in the phantom where the films were positioned. Shielding effects and the heterogeneities in the human body and the applicators are entirely neglected in the dose calculations performed by the commercially available TPS [12]. This will lead to a mismatch between the planned and delivered doses to the tumour and organs at risk. To mimic the effect of the heterogeneity, Sinnatamby et al. [28] has suggested a method using a stack of Gafchromic EBT2 films in a Poly Methyl Methacrylate phantom (PMMA) by placing stainless steel catheters below the film stack. The results in this experimental study were compared with that of the AcurosTM BV heterogeneity algorithm. The study concluded that stack films could be used for QA in HDR brachytherapy to imitate heterogenic structures.

Recently, three dimensional (3D) printing technology was introduced for dosimetric studies using custom applicators in HDR brachytherapy [36]. Oare et al. [26] has found the relationship between the radiation doses and its uncertainties in 3D printed PMMA and Acrylic Butadiene Styrene (ABS) plastics used for radiochromic film calibration with HDR ^{192}Ir brachytherapy sources. This study proves that 3D printed plastics can be used successfully as a substitute for water in HDR ^{192}Ir brachytherapy dose verification studies. However, uncertainties related to scattering and position of the source should be estimated with high

precision accurately determined dose delivered.

3.1.2. Verification using Ionization chamber

Ionization Chamber (IC) is considered a standard instrument that provides absolute dose measurements [37,14]. The measurements of ICs are influenced by dose–response, dose rate, beam energy, radiation quality, radiation beam direction, dosimeter stability at high temperature and humidity [38]. ICs require sufficient volume (about 250 cm^3 or more) for adequate sensitivity as low air kerma rate sources are used in brachytherapy treatments. In literature, HDR dose verification studies were reported with the use of different types of ICs [39–42]. Air-filled ICs were considered as standard detectors in brachytherapy dosimetry because of easy dosimetric characterisation, less effects raised by recombination effects and long-term stability. However, these detectors reportedly have low spatial resolution as they show a poor response in smaller active volumes [43].

A cylindrical brachytherapy phantom made of Solid Water^{TM} was developed by [37] and used for dose verification in HDR brachytherapy TPS. A MC simulation study using PENELOPE code was also performed to compare experimental and TP dose distribution. The results confirmed that the phantom model could be used in QA procedures as well as the dose verification of HDR treatment plans with ±2% and ±3% threshold level respectively.

3.1.3. Verification using two dimensional (2D) ionization array(IA)

The feasibility of real-time dose verification with MatriXX 2D ionization array (IA) was studied by Yewondwossen et al. [39] and Jozef et al. [44]. These studies were conducted to determine the suitability of MatriXX 2D arrays in measuring absolute and relative dose distributions during ^{192}Ir HDR brachytherapy treatments. The phantom used in Yewondwossen et al. [39] study was built up with a water-equivalent material. It has greatly helped to get full scattering conditions in the targeted area. The phantom was scanned using a cone-beam computed tomography (CBCT) scanner and the dose distributions generated by the TPS were compared with measured dose distribution of a ^{192}Ir brachytherapy HDR source in IBA Dosimetry OmniPro-I'mRT software. The gamma (γ) index was 2 mm (delta dose) and 3% (distance criterion). The mean difference between measured and calculated dose distribution was less than 3.7%. The agreement of dose distribution for different test plans was with greater than 94.5%. The study concluded that the MatriXX 2D IA was reliable to verify the dose distributions for the ^{192}Ir HDR brachytherapy source [39]. A similar study was carried out by Jozef et al. [44] and it too has confirmed the feasibility of the use of the MatriXX 2D IA. In their study, the gamma (γ) index was 3 mm and 3%. The agreement between the MatriXX measurements and TPS calculations were within ±10% [44]. The authors recommended that the source needs to be calibrated using an IC to confirm that primary source strength calibration is correctly updated in both the TPS and treatment delivery console computers prior to implementation [39]. The study concluded that source positioning corrections relative to MatriXX 2D ICs, the definition of the effective point of measurement and the energy response correction with respect to spectrum changes with depth are needed to be adequately addressed for the further improvement of this system [44].

A dosimetric study was conducted using a liquid-filled IC 2D array (PTW OCTAVIUS detector 1000 SRS (IA 2.5–5 mm)) to investigate the HDR intracavitary GYN treatment plan [14]. An air-filled 2D IC array (PTW OCTAVIUS detector 729 (IA 10 mm)) and EBT3 Gafchromic films were also used for comparison. All three detectors were placed at 2 cm from the applicator plane. Among the three detectors used, liquid-filled IC array (IA 2.5–5 mm) was identified as more sensitive to positional error compared to the other detectors due to high special resolution and self-attenuation. Therefore, the liquid-filled IC array is a promising dose verification detector system for HDR brachytherapy treatment [14].

3.1.4. Verification using Scintillation detectors

Scintillation detectors are made out of crystal material as such when radiation strikes this material it gives off photons of visible light. The light pulses generated are captured by photocathode, and they will be converted into electrical pulses. Several studies have proved the use of scintillation detectors in dosimetric verification in HDR brachytherapy over the past decade [46,47]. Therriault et al. [46] evaluated the accuracy of a plastic scintillation detector (PSD) for planned dose verification purposes. A green PSD with a diameter of 1 mm and length of 3 mm was used to measure the radiation dose surrounding the target organs during prostate ^{192}Ir HDR brachytherapy. The PSD is coated with carbon to protect the detector from external light. Light emitted from the PSD was transmitted to a red-green–blue photodiode, directed to a dual-channel electrometer. PSDs possess excellent water-equivalence, and additionally, they show linear response, high sensitivity and resistance to radiation damage which makes PSDs suitable in real-time verification [47]. The main disadvantage of a scintillation detector is the light created in the optical fibre when the radiation strikes it, called the stem effect light. Several techniques such as background subtraction, simple filtering, and chromatic removal can be used to minimize the stem effect and can be minimized through background signal [60]. The PSD system used in Therriault et al. [46] showed the ability to remove stem effect through the chromatic removal method.

Kertzscher et al. [47] used various inorganic and organic scintillator materials for online treatment verification during the dose delivery. Inorganic scintillation detectors (ISDs) show high efficiency, but they have a very poor water equivalent nature. Therefore they are not considered as very good dosimeters to be used in dose verification studies [60]. In this study stem effect was removed by subtracting the bare fibre's signal intensity measured without a scintillator volume from the ISD and PSD intensities. The stem signal was negligible for CsI: Tl-based ISDs. The results showed that ISDs based on a mixture of Y_2O_3:Eu and YVO_4:Eu are more suitable for HDR brachytherapy real-time verification. This dosimetric system is economical and easy to manufacture and handle [47]. This conclusion was consistent with the previous studies conducted in Molina [61], and Nakamura et al. [62]. The optimized packing density of the phosphor mixture in the scintillation detector, shortening of the fibre-optic cable and utilizing a photodetector with high sensitivity are few other methods that can be used to minimize the stem effect of the signal [63,64].

3.1.5. Verification using Flat panel detectors (FPDs)

Flat-panel detectors (FPDs) are commonly used for medical imaging purposes. Recently FPDs have been widely employed in the field of diagnosis and radiation therapy as a new advancement. Initially, FPD was designed as an electronic portal imaging device that can be utilized during HDR brachytherapy treatment. However, Smith et al. [48] have developed a TPS using FPDs and a solid water phantom which can be used in both pre-treatment imaging and source tracking during ^{192}Ir HDR brachytherapy treatment. The FPD was positioned under the patient's couch to detect the exit radiation from the water phantom placed on the couch during the treatment. The source positions were determined at each dwell position and compared with the corresponding planned source dwell positions [48]. The significant advantage of this dosimetry system is that it can determine the position of the source throughout the treatment delivery. It allows identifying where the source positions are relative to the applicator, and the dose distribution around the target can be easily obtained. FDP can detect deviations in brachytherapy treatment and ensure patient safety. In this study, the agreement between the measures source positions measured using the FPD and the planned source positions was found within to be 0.6 mm. It has proven that this dosimetric system can provide accurate dose verification specifically in clinical approaches. Nose et al. [49] used an FPD system of the fluoroscopic X-ray equipment for real-time dose verification of HDR ^{192}Ir source positions during treatment. Similar to Smith et al. [48] study, the source positions measured with the FPD were

compared with the planned source positions. This verification method can be used to conduct more practical real-time dose verification.

3.1.6. Verification using Semiconductor detectors

The use of semiconductor radiation detectors in brachytherapy has grown exponentially over the past decade [65,66]. The long-term development of silicon radiation detectors and their application in radiation therapy shows a good agreement with film dosimetry in spatial resolution and ICs in 2D dosimetry in real-time procedures [65]. Semiconductors have many advantages due to their small physical size, good energy resolution and easy pixilation for high spatial resolution. They show good accuracy in brachytherapy dosimetry studies, but their sensitivity changes with distance and they are not water equivalent [67]. Semiconductor detectors tend to underestimate the radiation dose when the distance from source to detector increases. Thereby, the correction factors should also be increased accordingly [65].

Metal–oxide–semiconductor field-effect transistor (MOSFET) detectors are widely used in brachytherapy dose verification studies. These dosimeters consist of silicon and are favourable in dosimetry verification due to small size and direct readout [68]. MOSFET dosimetry system for dose verification of ^{192}Ir HDR brachytherapy TP was investigated by Qi et al. [67] and the percentage deviations between the measured doses and the planned doses were below 5% for all the measurements. Further, MOSFET was used to calculate the actual delivered dose in patients during treatment [66]. In Persson et al. [50], a MOSFET detector was used to verify the dosimetric accuracy of HDR brachytherapy treatments in a custom-made water phantom. Even though the dose comparisons were below 3%, the measurements overestimated the TPS doses, which showed that the response of MOSFETs highly depends on the spectrum of photon energies and the phantom size [50]. These systems are sensitive to linear response and are often used in arrays to measure real-time dose distribution. However, significant limitations of MOSFET detectors include the absorbed-dose energy dependence, accumulated-dose and angular dependence, which leads to extensive characterization to reduce uncertainties associated with the detector's performance.

As a solution, diamond detectors were introduced for semiconductor detector dosimetry studies. They are predominatly designed to measure small field dosimetry of high-energy radiation beams. Dosimetric studies with diamond detectors are benefited with good stability, negligible dose-rate dependence, uniform energy response and low angular and temperature dependencies [69,70]. Kaveckyte et al. [71] has successfully used micro-diamond detectors in HDR brachytherapy dose verification, and it has shown a deviation of −1.3 to + 2.9% between the experimental and TPS calculations.

3.1.7. Verification using Thermoluminescent dosimeters (TLD)

TLDs are widely used in brachytherapy due to their relatively smaller size and high precision [72]. Further, the mean atomic number of TLDs matches the mean atomic number of the soft tissues. For most of the phantom studies, TLDs are used for point dose measurements [72,73,51]. Hence the measured dose may not always represent the clinical significant dose to the OAR. It requires repetition and measurements at several points, which is one drawback of using them as dosimeters.

In Moura et al. [18] study, a heterogeneous phantom was designed using Virtual Water™ (VM), BR50/50™, cork, and aluminium arranged in 11 heterogeneity configurations to verify the TPS algorithms used in the HDR brachytherapy [18]. TLD-100™ is used to measure relative responses and compared with Gafchromic EBT3 film, an Exradin™ A1SL IC, MC code and TPS. TLDs were placed in the center of the phantom volume and for each phantom setup, five TLDs were used. Measurements performed in the heterogeneous setups were normalized to the dose values measured in the homogeneous Virtual Water™ setup. Dose distribution in the phantom study showed good agreement with the simulations and TPS calculations. Differences in the dose responses were evident in the experimental results due to the heterogeneous effect. This study highlighted the importance of accounting for the effect of heterogeneity in HDR TPS based on MBDCA [18]. However, compared to EBT3 films, TLD and IC have shown slight deviations (< 0.5%) from the TPS calculations. EBT3 films are more susceptible, compared with other dosimeters used in this work, when low-density materials are employed in the phantom. The energy dependent nature of the EBT3 films result in higher uncertainty than TLDs and ICs due to the fact that scattering photons are dependent on the medium composition and material thickness. This indicates that TLDs can be used successfully for dose verification methods in heterogeneous environments. Bassi et al. [59] conducted a similar study to develop a novel procedure for a dosimetric audit of ^{192}Ir HDR units using a 3D printed water-equivalent phantom with Farmer Chambers, GafChromic EBT3 films and TLDs placed at known distances. The study concluded that 3D printers could effectively be used to model phantoms for a multicentre environment with different models of ^{192}Ir sources and different treatment planning systems.

Lucas et al. [51] developed a procedure to estimate the spatial dose distribution around a HDR ^{192}Ir brachytherapy source in a water medium. The developed technique is based on calculations and measurements of MC in air and water using TLD-100H detectors [51]. The TLD detector underestimated the mean value near the source (at about 1 cm) because of its size and relatively high dose gradient near the source. These variations can be decreased by limiting positional variations in the vicinity of the source.

Nikoofar et al. [52] study estimated absorbed dose in risky organs during brachytherapy treatment for oesophagal cancer in ^{192}Ir HDR remote afterloading brachytherapy using an anthropomorphic phantom. Phantom constructed using natural bone and a mixture of paraffin wax with sodium chloride as an impurity for soft tissue. The dose measured by TLDs at critical organs such as eyes and parotid, submandibular, and thyroid glands showed higher than TPS dose distribution while other organs such as trachea, spine, and manubrium of sternum received approximately the same dose as was calculated by TPS. TLDs were selected as the dosimeter owing to the accuracy in vivo measurement tool to evaluate dose delivery in brachytherapy systems and they can be easily handled. The deviations were mainly due to ignoring tissue inhomogeneity in the TPS algorithm. Further, the dose distribution in distant regions was due to scattering radiation and in closer regions was due to primary radiation [52]. The results reflect that the TLDs can be successfully incorporated to the invivo brachytherapy dose verification studies.

3.1.8. Verification using optically stimulated luminescence dosimeters (OSLDs)

The mechanism of OSLDs is very similar to TLDs which can be applied in dosimeter studies. However, OSL dosimetry has recently seen some significant developments that have led to its increasing use in real time measurements in dose verification [74]. In the Silva et al. [53] study, a prototype phantom made of PMMA was developed to study the bladder dose during GYN HDR brachytherapy and the dosimetric results were obtained using both radiochromic film and OSLDs placed on the artificial bladder wall 3D printed using computed tomography (CT) images. The applicators were placed according to the original CT image. This method had allowed studying the behaviour of the dose on the bladder surface during intracavitary brachytherapy procedures more accurately [53]. One of the main challenges of selecting appropriate dosimeters in vivo dosimetry studies to verify the dose delivery is defining and localizing the dosimeters in the appropriate positions in the OARs. The position of the dosimeters in appropriate locations is critical in predicting the side effects of the dose. This study has proven that OSLs can serve this purpose successfully. Dose distribution was obtained using both films and OSL detectors and the results obtained are in good agreement with all the deviations less than 10% compared to TPS calculations. However further studies were suggested to study the behavior of the dosimetry system on high gradient dose regions.

3.1.9. Verification using Gel dosimetry

Practical issue in film dosimetry and TLD dosimetry is the ionisation happens through the air gaps within the dosimeter array setup which leads to change in the amount of absorption [75,76]. As a solution for this problem, during the last few decades, number of investigations regarding gel dosimetry in brachytherapy has rapidly expanded [77–79]. Most of the researchers have discovered the ability of polymer gels to study the dose distributions around a HDR source [22,55,58]. Hence gel dosimetry can be used as a convenient tool for QA. Gel dosimetry has many beneficial properties that can facilitate the dosimetry of radiation therapy, especially in situations that are poorly handled with conventional dosimeters. It possesses the ability to measure complex 3D dose distributions and integrate dose accurately despite dependence on the dose rate. Some other characteristics of gel dosimetry include tissue-equivalence, high spatial resolution and lack of energy dependence over most of the kilovoltage and megavoltage range [77].

Carrara et al. [79] evaluated the reliability of Fricke gel layer dosimeters (FGLDs) for measuring the distribution of the phantom dose generated by ^{192}Ir brachytherapy source. The doses obtained were compared against measurements performed with TLDs and TP calculations. Radio-chromic Fricke gel layers with defined thickness surface and tissue equivalence properties were used. FGLDs were prepared in the laboratory by infusing a ferrous sulphate solution and the metal-ion indicator Xylenol Orange (XO) in a tissue-equivalent gel matrix. When the FGLD is exposed to ionizing radiation XO/Fe^{3+} complex is formed by the conversion of ferrous ions Fe^{2+} into ferric ions Fe^{3+}. This complex causes visible light absorption with a yield proportional to the absorbed dose, which can be evaluated by placing the dosimeter on a planar illumination source and by detecting their optical transmission images at the correct wavelength using a charge-coupled device (CCD) camera. Results have shown that FGLDs are a promising tool to measure 3D dose distributions in HDR brachytherapy [79].

However, the study showed that Fe^{2+} and Fe^{3+} ions diffusion result in blurring the dose profiles close to the brachytherapy source. Therefore, many researchers studied various polymer gels to limit the diffusion problem and new types of polymer gels were introduced to the dosimetry studies, including MAGIC gel (Methacrylic and Ascorbic acid in Gelatine initiated by copper) and nanoclay-based radio-fluorogenic gel[80–82].

Recently a dose verification study was conducted by Watanabe et al. [54] who investigated the characteristic of a Nanoclay-based Radio-Fluorogenic Gel (NC-RFG) dosimeter is a fluorescent gel dosimeter using dihydroergotamine 123 hydrochlorides (DHR 123) fluorescent probe. A clinical plan was evaluated for the 2D dose distribution at multiple source positions. The dose distribution measurement was compared with the TPS calculation. The authors reported that the NC-RFG dosimeter was successfully used as a QA tool in HDR brachytherapy. Moreover, NC-RFG dosimeter performs well compared to conventional gel dosimeters in various aspects, such as diffusion, dose rate dependence and inhibition of oxygen-induced reactions [54]. Furthermore, this dosimetry system is more useful in clinical practice as the dose data can be obtained easily within a short time after irradiation.

Senkesen et al. [55] study evaluates the 3D dose distributions of ^{192}Ir brachytherapy source for irradiation with single and multiple dwell positions using a normoxic gel dosimeter. The obtained results were compared with TPS calculations and the results proved that Gel dosimetry has the potential to obtain 3D dose distributions for HDR ^{192}Ir brachytherapy sources with a close agreement to TPS [55]. Many studies have proved the effectiveness of gel dosimetry in brachytherapy dose verification studies due to their polymerization, oxidation-state change or colour changing properties during exposure to ionizing radiation [79,54]. Additionally, gel dosimeters can store data permanently which make them suitable for the performance of dosimetry at remote locations and gel dosimeters are relatively safe to manufacture and handle [77]. The effort to optimize the use of gel dosimetry in the brachytherapy dose verification study has been an active area of research. Short summary of the dose verification study information provided in literature published between 2010 and 2020 is given in Table 2.

3.2. Verification using Monte Carlo(MC) simulation

MC codes are being widely used as a tool for verification of the dose calculated on patient anatomy and phantoms [83,84,58]. Commonly used MC codes for interstitial brachytherapy dosimetry are BRACHYDOSE, MCPI, GEANT4, EGS, MCNP, Williamson's PTRAN and TOPAS [72,85–87]. The MC codes are used to build the photon and electron brachytherapy source models validated using different dose parameters according to the AAPM TG-43 protocol [11]. A detailed 3D model of specific source geometry can be obtained for dose calculations in brachytherapy treatment [88]. Further, the dosimetric parameters such as air-kerma rate(S_k), dose rate constant($\wedge$), and particle fluence at a geometric position can be simulated. These parameters are crucial elements in TP. Dosimetric characterization of BEBIG ^{60}Co source has been carried out using EGS5 MC code by Badry et al. [89]. In their study, a 2D cartesian dose distribution in a water phantom was obtained and compared with previous studies. Similar studies were conducted with other MC codes; egs-brachy MC by Reddy et al. [57], GEANT4 by Granero et al. [90], PENELOPE (version 2011) by Guerrero et al. [91], MCNPX by Elboukhari et al. [92] and TOPAS by Wu et al. [93]. Table 3 summarizes the HDR brachytherapy dose verification studies conducted via computational methods in literature published during last 10 years.

Reddy et al. [57] compared the experimentally measured dose parameters of a BEBIG ^{60}Co (Co0.A86) HDR source in a water phantom with egs-brachy MC calculated values. A cylindrical phantom with liquid water was simulated, and the scoring region was divided into small voxels to obtain the dose distribution. The density and temperature were set as recommended in TG-43. Further, the study suggested that the MC calculated dosimetric parameters could be used as inputs to the clinical dosimetry through TPSs. Similarly, in Granero et al. [90] study, an unbounded liquid water phantom was used as the global geometry and the dose distribution was obtained by using the Geant4 MC method when the source was at the centre of a spherical water phantom. A grid system composed of cylindrical rings of 0.05 cm thick and 0.05 cm high, concentric to the longitudinal source axis, was used to calculate the source's dose parameters and dose distribution. Guerrero et al. [91] used PENELOPE simulation code to calculate the dose rate. The source was kept inside a spherical geometry, and cylindrical voxels and spherical voxels were used to obtain the energy deposited in the water phantom. The study found that there were no significant differences between the two geometries. The limitations of TG-43U1 formalism are that it does not account for tissue heterogeneity, and the medium is water with uniform density. Brachytherapy dose calculation formalism is based on fixed radiation scatter and heterogeneity conditions in water medium [102,103]. Further, the TPS assumes that both applicator and inter source effects are negligible. MC simulations improve the TP compared to the TG-43 formalism by accounting for patient-specific radiation scatter conditions and the radiological effect of material heterogeneities differing from water medium [104]. Badry et al. [89] studied the radial dose function obtained in different mediums, including water, bone, lung, adipose tissue, breast and muscle. Results revealed the difference in the radial dose function of water with other mediums, highlighting these limitations of the AAPM protocol.

4. Discussion

Multi-energy release of the radioactive sources and the condition of maintaining the short dose fall-off, pose a huge challenge in estimating the dose distribution of a typical brachytherapy procedure. In general, TPSs are used to estimate the radiation doses received by the targeted area and the organs at risk before performing the actual treatment. TG-43 formalism used in TPS in HDR brachytherapy assumes that the source is immersed in a water medium. Additionally, TG-43 formalism ignores

Table 2
Short summary of the information provided in literature published between 2010 and 2020. (MD = Maximum Deviation; Exp = Experiment; Pha = Phantom; Sim: Simulation; MC: Monte Carlo; QA = Quality Assurance; TP: Treatment Planing; BT: Brachytherapy)

Year and Reference	Method	Purpose	Detector	HDR Brachy Source	Accuracy (MD)	Additional Information
2012 Yewondwossen et al. [39]	Exp (Pha)	Plan verification	MatriXX	Ir-192	3.7%	Performance of IC array for kV range was evaluated. Phantom was built with RW3 water-equivalent slabs.End-to end dosimetric procedure was developed for brachytherapy treatment.
2012 Jozef et al. [44]	Exp (Pha)	Plan verification	MatriXX	Ir-192	±10%	High measurement uncertainty. Further improvements required.
2018 Yoosuf et al. [14]	Exp (Pha)	TP QA	IA 10 mm IA 2.5–5 mm EBT3	Ir-192	0.2%± 1.6% 1.8%± 1.0% 1.5%± 0.81%	Estimated standared uncertainties for EBT3, IA 10 mm and IA 2.5–5 mm are 4.75%, 2.31% and 2.19% respectively
2011 Aldelaijan et al. [30]	Exp (Pha)	TP QA	EBT2	Ir-192	4.12% (>1 Gy)	Solid waterTM material was used. Parallel-opposed beam geometry and green channel of the scanned film piece images enhanced the accuracy.
2016 Gholami et al. [24]	Exp (Pha)	TP QA	EBT	Cs-137	±6%	Accuracy of themeasurements was checked at some reference points and also for isodose lines.
2011 Micke et al. [45]	Exp (Pha)	TP QA	EBT2	Co-60	±2%	Multichannel dosimetry with EBT2 showed vital benefits over single channel dosimetry.
2018 Sinnatamby et al.[28]	Exp (Pha)/ MC	TP QA	EBT2	Ir-192	±2%	Clinical needs needed to be addressed. Should consider the normal organ dose tolerances and spatial uncertainty.
2012 Uniyal et al. [31]	Exp (Pha)	TP QA	EBT2	Ir-192	±3.9%	More productive method than TLD dosimetry at discrete and distant positions. Advantages: reproducibility, easy to use and cost effectiveness.
2013 Palmer et al. [29]	Exp (Pha)	Plan verification	EBT3	Ir-192/Co-60	±3%	EBT3 film with multi-channel analysis is suitable for of QC procedures, commissioning checks and dosimetric audits.
2014 Palmer et al. [27]	Exp (Pha)	Plan verification	EBT3	Ir-192	±3%	Triple-channel dosimetry can be employed to minimise uncertainty.
2013 Austerlitz et al. [37]	Exp (Pha)/ MC	Plan verification	A1SL IC	Ir-192	±3%	Brachyphantom is agreeable in QA and dose verification studies. It provides fast and independent determination of the dose with less uncertainty. water
2011 Therriault et al. [46]	Exp (Pha)	Plan verification	PSD	Ir-192	2%-3%	Stem effect was removed using a chromatic removal method.
2017 Kertzscher et al.[47]	Exp (Pha)	Plan verification	ISD	Ir-192		Cost effective method. Further modification need for temperature and energy dependence corrections.
2016 Smith et al. [48]	Exp (Pha)	Plan verification	FPD	Ir-192		System can serve in both imaging and source tracking purposes. Can be successfully utilized in real time brachtherapy procedures.
2019 Nose et al.[49]	Exp (Pha)	Plan verification	FPD	Ir-192	0.2%	Establish the safety in real-time dose verification studies.
2018 Persson et al. [50]	Exp (Pha)	TP QA	MOSFET	Ir-192	2%–7%	Recommends addressing the beam quality correction factors from phantom dimensions.
2012 Lucas et al.[51]	Exp (Pha)/ MC	Plan verification	TLD	Ir-192	7%	Notable variations were observed at points close to the source due to the large size of TLDs. These can be addressed by modifing the experimental setup.
2015 Nikoofar et al. [52]	Exp (Pha)	TP QA	TLD	Ir-192	7%	Deviations in the absorbed dose close to the source were due to primary radiation whereas the deviations at distant positions were due to scattered radiation.
2015 Moura et al. [18]	Exp (Pha)/ MC	TP QA	TLD, EBT3,A1SL IC	Ir-192	11.5%	Shown the importance of using heterogeneous phantom in HDR BT dose verification.
2015 Silva et al.[53]	Exp (Pha)	Plan verification	OSLD, EBT3	Ir-192	<10%	This study has introduced an accurate dose verification method to obtain the dose on the bladder surface during Intracavitary BT procedures for cervical cancer patients.
2020 Watanabe et al. [54]	Exp (Pha)	TP QA	NC-RFG	Ir-192	2%	Successfully addressed the gel diffusion. Dosimetry system provides data within short time after irradiation, which is beneficial in clinical application.
2014 Senkesen et al. [55]	Exp (Pha)	Plan verification	MAGIC	Ir-192	<10%	Deviation is due MRI artifacts and heterogeneity effect. Further studies needed to improve gel preparation,imaging and analysis of the gel phantom.
2013 Oshaghi et al. [56]	Exp (Pha)/ MC	Plan verification	TLD	Ir-192	<8%	MCNP5 code was used for the MC study. Results showed good agreement between simulation,TP and experimental studies.
2019 Reddy et al. [57]	Exp (Pha)/ MC	Plan verification	TLD, EBT2	Co-60	2%	egs–brachy code was used for the MC study. MC calculated dosimetric parameters can be used as inputs to the clinical dosimetry through TPS.
2017 Pappas et al. [58]	Exp (Pha)/ MC	Plan verification	TLD, EBT3, plastic 3D dosimeter	Co-60	2%	MCNP v.6.1 code was used for the simulation. Out of the detectors used in the study, radiochromic films was proven as the best candidate for the experimental MBDCA validation.
2020 Bassi et al.[59]	Exp (Pha)	Auditing	Farmer chamber, TLD, EBT3	Ir-192	2.5%	Customised 3D printed water-equivalent phantoms can be effectively used in verification for a multicentre environment with different source models and TPSs

Abbreviations: MatriXX–IBA MatriXX 2D array; IA 10 mm–PTW OCTAVIUS detector 729; IA 2.5–5 mm–PTW OCTAVIUS detector 1000 SRS; EBT3–EBT3 Gafchromic film; EBT2–EBT2 Gafchromic film; PSD–Plastic Scintillation detector; ISD–Inorganic scintillator detectors; FPD– Flat panel detector;

MOSFET–Metal–oxide–semiconductor field effect transistor; OSLD–Optically stimulated luminescence dosimeters; FGLD–Fricke gel-layer dosimeters; NC-RFG–Nanoclay-based radio-fluorogenic gel; MAGIC–Metacrylic and Ascorbic Acid in Gelatin Initiated by Copper.

Table 3
Short summary of computational methods in literature published between 2010 and 2020.The parameters S_k/A and $\wedge$ are given in the units of $10^{-7}UBq^{-1}$) and $cGyh^{-1}U^{-1}$ respectively.

Year and Reference	MC Code	HDR BT source	S_k/A	$\wedge$	Statistical Error%
2018 Badry et al. [89]	EGS5	BEBIG ^{60}Co, Co0.A86	3.042	1.092	0.7
2014 Guerrero et al. [91]	PENELOPE	BEBIG ^{60}Co, Co0.A86	3.046	1.094	< 0.3
2020 Elboukhari et al. [92]	MCNPX	BEBIG ^{60}Co, Co0.A86	3.030	1.092	< 1
2021 Wu et al. [93]	TOPAS	Varian GammaMed Plus ^{192}Ir	1.014	1.11	< 0.1
2013 Anwarul et al. [94]	EGSnrc	BEBIG ^{60}Co, Co0.A86	3.039	1.097	< 0.5
2015 Campos et al. [95]	EGSnrc	BEBIG ^{60}Co, Co0.A86	-	1.108	< 0.5
2016 Naeem et al. [96]	EGSnrc	MicroSelectron v2 ^{192}Ir	0.9762	1.108	0.2
2014 Belousov et al. [97]	GEANT4.9.6	^{169}Yb	-	1.140	< 0.5
2018 Lei et al. [98]	GEANT 4	GZP6 ^{60}Co	3.004	1.088	< 0.2
2017 Almansa et al. [99]	PENELOPE 4	Flexisource ^{60}Co	3.046	1.0942	< 0.4
2015 Thanh et al. [100]	MCNP 4	M-15 Ir-192	0.982	1.112	< 0.3
2010 Casado et al. [101]	PENELOPE	Varisource VS2000 ^{192}Ir	1.015	1.10	< 2

the presence of air or other scatter objects such as applicator, radiographic contrast, shielding, contrast solution perturbations, and tissue inhomogeneity effects. Inaccuracies in the estimated dose distributions which arise from the aforementioned assumptions of TG-43 formalism may produce hot spots outside the target leading to significant damage to the normal tissue and cold spots with the target leading to under dosing, compromising treatment outcomes. Therefore, more accurate verification of dose calculation and reliable QA procedures are needed to optimize the therapeutic index. Approaches of dose verification which are based on experimental and computational studies can successfully address the issue.

Experimental dose verification studies are conducted by employing in–house or commercial phantoms and placing suitable dosimeters in order to measure the dose distribution. In–house phantoms mimic the human tissue and its inhomogeneity, an essential factor which is ignored by the commercial phantoms and the TG-43 formalism. Radiochromic film, IC systems and scintillation detectors have been used commonly in the early studies of HDR dose verification systems during the period of 2010 to 2020. However, the size of these detectors are inconvenient to utilize in real time dosimetry. Hence, semiconductor detectors, TLDs and gel dosimetry became more popular as alternatives. Advantages and disadvantages of different dosimetry systems are summarised in Table 4 According to the studies referred in this survey, TLDs can be identified as a popular and efficient candidate for brachytherapy dose verification studies due to its high precision, good linear response to the radiation and low cost. Furthermore, Gel Dosimetry can be recognized as the latest advancement in HDR dose verification studies. The biggest advantage of utilising this method is that, the gel medium can be moulded to any desired shape or form easily. Moreover, there is no need for energy corrections as the gel medium is nearly water equivalent.

Computational dose verification methods are executed by employing the MC codes which can simulate the random events of radioactive decay and energy deposition in human tissue. MC codes provide the facility of modelling the radiation sources and the treatment environment in standard geometries to obtain the dose distributions. The most efficient way of simulating the realistic treatment planning conditions of a particular patient is to use a voxelized phantom created by incorporating real-time images of the targeted areas in the patient's body. Over the years, several MC codes have been used to simulate the dose distributions and calculate the dose parameters. Even though, the algorithmic structure of these MC codes are different from each other, they show a good agreement in dose parameters. In addition, MC simulations can be used to determine the correction factors necessary to convert the absorbed dose in an irradiated medium to the absorbed dose in water [105].

As the brachytherapy treatment procedure develops, the verification methods also have evolved during the past decade allowing optimal clinical effects on the tumor, while sparing healthy surrounding tissues. Advanced algorithms such as MBDCA are used to calculate and optimize the dose distribution. Both experimental and reference dosimetry data

Table 4
Advantages and limitations of different dosimetry method for use in brachytherapy.

Dosimetric System	Advantages	Limitations
Radiochromic film [24–27,34,35,28]	High spatial resolution, consumable cost, water equivalence	Characterization of film, need scanners to achieve the dosimetric results.
Ionization chamber [37,39–42,14,38]	Can be calibrated to provide a near absolute dose measurement	High voltage to work, Due to finite dimensions cannot be used in vivo, Need dose ionization conversion factors
Scintillator detectors [46,47,60–64]	Plastic: small-volume detectors, reproducibility, continuous sensitivity, linearity of response, high degree of water-equivalence, resistance to radiation damage, real-time operation. Inorganic: high efficiency	Plastic: expensive, stem effect, highly susceptible to background light. Need to use background subtraction counter, which requires another set of fibers and PMT Inorganic: poor water-equivalence
Semi conductor detectors [65,66,50,71]	High spatial resolution, high efficency in 2D real time dosimetry, small size, ability of integration with readout electronics.	sensitivity changes with distance, not water equivalent
TLD [73,51,18,52,53]	Small size and available in different forms, high precision, low cost, re-usability	Need to be annealed to erase the residual signal used for point dose measurements. Thus it requires repetition and measurements at several points. correction factors have to be applied, such as those for energy, fading and dose response non-linearity
Gel dosimeters [55,58,80–82,54]	Ability to measure complex 3D dose distributions tissue equivalent and can be moulded to any desired shape or form nearly water equivalent no energy corrections are required for photon and electron beams can store data permanently relatively safe to manufacture and handle.	Continual post-irradiation diffusion of ions, resulting in a blurred dose distribution.

obtained using MC simulation are used to verify MBDCA-based predictions. Dose verification is important to check the dose distributions calculated in patient-specific scatter and material heterogeneity conditions. Moutsatsos et al. [106] study has found that Oncentra-ACE MBDCA based TPSs, shows good agreement within corresponding uncertainties in experimental methods which used TLDs & radiochromic films and MC–calculated dosimetry results. Famulari et al. [17] study has verified the RapidBrachyMC based TPS by comparing the results to other MC calculation codes and film measurements. The AcurosTM BV takes into consideration absorption through the catheter, tissue inhomogeneity, and helps in more accurate dose computation and defines actual doses delivered [28]. In a recent study, brachytherapy dose comparisons were conducted using three different dose calculation algorithms: BrachyDose MC code, Eclipse TG-43 dose calculation tool and Acuros®BV MBDCA. Further, the study has shown that Acuros®BV and BrachyDose agreed well and TG-43 formalism overestimated the dose to critical organs. Thus, this comparison can be used as a guide to make corrections on the actual dose delivery [107]. Pappas et al. [58] evaluates the feasibility and practicality of experimental Advanced Collapsed cone Engine (ACE) MBDCA validation using different dosimetric systems. Point, 2D and 3D dose distribution were obtained using TLDs, EBT3 radiochromic films and PRESAGE dosimeters respectively. Radiochromic films appear to be the best candidate for the experimental MBDCA validation in this work. Apart from MC methods, recently, MATLAB code (MathWorks, Massachusetts, USA) has been used to develop a novel tool called MaxiCalc for source tracking treatment verification in HDR brachytherapy Hanlon et al. [108]. MaxiCalc can be used to calculate both doses, and DVH (Dose Volume Histogram) indices with any clinical HDR brachytherapy source tracking system [108].

Nevertheless, in literature it is shown that a dose verification procedure which uses both experimental and MC methods is very much effective in minimizing the errors and optimizing the treatment plan. An experimental study based on a phantom with tissue equivalent properties and human anatomy helps to mimic the exact environment of exposure and to identify the over and under irradiated regions. Furthermore, MC simulation study can be used to simulate the tissue inhomogenity and its impact on the treatment. The effectiveness of the brachytherapy treatment depends on the accuracy of the TPS. However, even a small change in the estimated dose can make a huge difference in the patient's actual treatment plan. To eliminate this issue and to generate more accurate TP conditions, voxelized phantoms can be built up using medical imaging techniques such as CT and magnetic resonance (MR) images. Development of medical imaging techniques is considered as one of the significant advancements in brachytherapy TP which enable to get 2D and 3D dose distributions in the TP process. TPS along with a proper dose verification method pave a way to get an optimized dose distribution and ultimately to achieve an effective treatment for the patient.

5. Conclusion

Verification of the dose distribution during brachytherapy treatment through an independent method helps to optimize the treatment plan. By using well designed experimental and MC dose verification systems, radiation doses delivered to the patient can be estimated properly. It helps to yield the actual dose received by the patients without any over or under estimations. Additionally, they provide possibility of QA and specific QC of the brachytherapy treatment. These techniques make the treatment procedure more efficient by obtaining the dose distributions in real-time and actual clinical situations. However, further improvements are required in dose verification methods to cater the rapid developments in clinical and scientific techniques related to brachytherpy treatment.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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