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Section A-Research paper

Improved methods for dosimetry of high-dose rate brachytherapy (HDR-BT)

Abduallah Odeh Dwairej[1,*], Hamad Yahia Abu Mhanna[2] and Hanan Fawaz Akhdar[3,*]

[1] Department of Radiography, Princess Aisha Bint Al-Hussein College of Nursing and Health Sciences, Al-Hussein Bin Talal University, Ma'an, Jordan; 0903003@ahu.edu.jo

[2] School of Physics, Universiti Sains Malaysia, Penang 11800, Malaysia;hamadabumhanna@gmail.com

[3] Physics Department, College of Science, Imam Mohammad Ibn Saud Islamic University (IMSIU), Riyadh 13318, Saudi Arabia; hfakdar@imamu.edu.sa

* Correspondence: 0903003@ahu.edu.jo(A.O.D.);hfakdar@imamu.edu.sa (H.F.A.)

Abstract: This paper offers a comprehensive review of dosimetry in high dose rate brachytherapy (HDR-BT), in terms of the recent practical dosimetry techniques and systems that are utilized for radiation delivery and dosage verification. This article presents the novel models in HDR-BT for a variety of cancer including the three-dimensional (3D) image-based dose-specification techniques. The performance of HDR-BT treatment entails positioning the radioactive sources proximate to the region of interest to achieve the delivery of high radiation doses to the tumor area. Dose delivery for brachytherapy adheres to the inverse square law where rapid attenuation or dissipation in radiation results in negligible impact on the contiguous healthy tissue or organs at risk (OAR). Thus, it is critical that a sharp decline in the distribution of radiation dose proximate to the HDR source is maintained. By appropriately deploying well prepared experimental and MC dose verification systems, doses of delivered radiation can be accurately determined, thus achieving the precise measurement of dose received by the patients devoid of mis-estimations. Hence, a detailed synopsis of the various verification (experimental and computational) methods was presented. This review summarizes the studies performed in recent times on HDR-BT dose verification and optimization as well as their benefits and constraints. The utilization of HDR-BT combined with imaging (computed tomography (CT), magnetic resonance imaging (MRI), intraoperative ultrasonography) was also discussed. Also given attention in this review are current dosimetry methods and clinical outcomes of HDR-BT in the treatment of various cancers.

Keywords: High dose-rate brachytherapy (HDR-BT); Dose calculation; Dose verification,dosimetry, Dosimetric accuracy

1. Introduction

High dose-rate brachytherapy (HDR-BT)is an efficient and accurate hypofractionated radiation delivery mechanism. The efficiency of this technique is largely attributed to its exceptional conformity and sharp decline in the radiation dose distribution away from the target volume. HDR-BT can be utilized for the effective treatment of cancer through the localized or targeted delivery of high radiation doses (>12 Gy/h), thus enhancing target treatment of cancerous cells and sparing healthy organs. Its efficacy is outstandingly high for large clinical targets with intricate topologies (Mendez & Morton, 2018; Guthier et al., 2020). HDR-BT is conducted by means of the remote afterloading system (RALS) to directly deliver a guarded radioactive source in the proximity of a tumor (Watanabe et al., 2022). Brachytherapy utilizing RALS of a solitary HDR source began several decades ago. Following its clinical initiation, use of the system expanded fast in the advanced world, evolving into a highly appealing technique for the treatment of cancer. In the last 30 years, the utilization of HDR-BT has considerably risen as compared to low dose-rate brachytherapy (LDR-BT). HDR-BT is presently the main BT treatment protocol or approach in a lot of countries (Tanderup et al., 2014; Patankar et al., 2015). Nonetheless, equivalent local control and survival have been reported for

both LDR-BT and HDR-BT (Romano et al., 2017), although the implementation of HDR-BT was shortly accompanied by a transient rise in the prevalence of severe toxicity (Romano et al., 2017). This temporary increase in severe toxicity associated with HDR-BT is a consideration in the implementation of novel technologies and advancements, which has led to the inclusion of magnetic resonance imaging (MRI) into the workflow of image-guided BT (IGBT).

The high specific activity of HDR radioactive sources facilitates the targeting of HDR on the tumour and shorter treatment duration, and the reduction in the size of source (microsource) that can be easily inserted into tissue (IAEA, 2015). An additional benefit of HDR-BT is the capacity to modify the duration it takes for a source to stationary, which is referred to as dwell time of the stepping source, to enable the close matching of dose distributions with the target volume. However, uncertainties in dosimetric accuracy are an issue with HDR-BT, but techniques were introduced to enhance the conformation of radiation dose to the prescribed projected dose distribution. Dosimetric accuracy of HDR-BT may also affect the attaining of clinical therapy goals, tumor control, and reduced toxicity of healthy tissue, attributable to the gradient of the plots for the effect of clinical dose. The complexity associated with dosimetry is more complicated in brachytherapy as a result of short treatment lengths, elevated dose gradients, and orders of magnitude difference in dose deposition across target volumes (Palmer et al., 2012). Moreover, HDR-BT is encumbered by its requirement of invasive procedures under anesthesia for the insertion of multiple metallic needles (Fukuda et al., 2014). In addition, the protracted bed rest needed after the procedure can increase the risk of infection or thromboembolism.

HDR is typically described as a dose delivered at a rate >12 Gy/hour, but is considerably higher most times, and frequently >1 Gy per minute (Mendez & Morton, 2018). HDR-BT compensates for the challenge of ineffective dosimetry that is associated with LDR implantation, which is attributable to seed loss or dislocation. Since the implementation of HDR involves the emplacement of the catheters, there is a higher assurance of consistency between the delivered and intended doses. The dosimetry consistency provided by HDR exceeds that of LDR, with lower variation in target coverage and lesser dose proportionate to rectum, bladder and urethra (Major et al., 2017). To fully highlight the current state of HDR-BT, this paper reviews existing functional techniques utilized for HDR-BT dosimetry, which includes research on the determination of dose rate fields in the proximity of brachytherapy sources, the capacity of treatment planning systems (TPS), the efficiency of treatment units, and dose verification techniques of dose delivery. This review evaluates the techniques in HDR-BT dose verification utilized in recent times to present a synopsis of advancements relating to the application of models to optimize HDR dose. This review also draws attention to topical and contemporary research on the current dosimetry methods and clinical outcomes of HDR-BT in treatment of cancer for various organs to reflect the dynamism on the ongoing research and development in the subject.

2. Methodology

2.1. Design

This study adopts a systematic-descriptive method to provide a comprehensive overview of the enhanced methods for dosimetry of HDR-BT. The review was conducted according to the Cochrane book and reported utilizing preferred reporting items for systematic reviews and meta-analyses (PRISMA) checklist (Moher et al., 2009). The research materials are sourced through a secondary data collection method using journals, published textbooks, and other important data sources.

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2.2. Inclusion and exclusion criteria

The review squarely pays attention to research published following 2000, whereas publications prior to 2000, letters to editors, and poor quality studies published in non-peer reviewed and not properly indexed journals as well as those written in non-English language were not incorporated.

2.3. Search strategy and selection of studies

Relevant literature radiation on dose distribution and dose verification studies in HDR-BT was reviewed, including articles analyzing HDR-BT related theories, methodology, novel research, and dosimetry practices in HDR-BT. The authors concentrated on SCOPUS-indexed publications (published in Science Direct, Springer, Elsevier etc),b PubMed papers and a small number of papers in Google Scholar with high citations. Various key words were used for the search, including "high dose rate brachytherapy (HDR-BT)", "Dosimetry", "Dosimetry of high dose rate brachytherapy", and "Dose recommendations for HDR-BT". Medline and Embase databases were also searched. The studies selected according to the inclusion criteria were thoroughly analyzed, while duplicate articles and those with only abstract proceedings were deleted. The titles and abstracts of the studies were first evaluated with aim of removing redundant or unrelated cases. The full texts of pertinent studies were then assessed for eligibility. The data extracted from the selected studies comprise: names of authors, methodology, year of publication, results, inferences, deduction, limitations and recommendations.This extracted information was complemented through the review of reference lists.

3. Components of HDR-BT

Brachymetry is utilized as an essential element in the treatment of cancer for close to 100 years. The performance of brachytherapy was improved by advances in afterloading units and development of novel radioisotopes. Presently, brachytherapy is typified by technical innovations that include: channel expansion in remote afterloading devices; creating radioactive microsources; producing novel algorithms for automated TPS and dosimetry, enhancing imaging techniques and incorporating sectional imaging. The treatment unit of an HDR facility requires a sufficiently sealed container and a remote afterloading equipment to prevent subjecting the operators to direct exposure. A remote afterloading system comprises an air-pressured or motor driven source transporting system that facilitates the automatic transfer of a radioactive source from the protected safe to the respective treatment applicator. The components of commercially obtainable HDR-BT afterloading units include: high dose radioactive source, applicators, control console, afterloader unit (treatment unit), and X-ray catheters, and TPS.

Photons and β radiation are the products emanating from Brachytherapy sources. In addition, the neutron emitting sources are utilized in a small number of specific conditions (Devlin, 2015). The commonly utilized brachytherapy sources include ^{60}Co, ^{137}Cs, ^{192}Ir, ^{125}I, ^{103}Pd and ^{90}Sr/^{90}Y. The selection of the suitable radiation sources for treatment requires being cognizant of the source power, energy and the kind of emitted radiation. Early on, ^{226}Ra and ^{222}Rn were typically utilized in brachytherapy steps, although discarded because of radiation safety issues (Suntharalingam et al., 2005). HDR-BT is composed of a radioisotope with high specific activity that is needed to concurrently realize the HDR and offer a miniature source dimension as a pre-requisite for intracavitary and interstitial BT. ^{192}Ir is extensively utilized for HDR BT due to its characteristically high specific activity (330 MBq/mm), relatively low γ energy (approximately 0.375 MeV), and a fairly short half-life (73.8 d). Presently, majority of HDR remote afterloaders employ a solitary ^{192}Ir source with a specific activity of about 370 GBq, and active length and diameter of around 3.5 mm and 0.5 mm, respectively. When encapsulated, the length and diameter of the source increase to approximately 5 mm long (can reach 10 mm in some cases) and <1.5 mm respectively, depending on the commercial model.

The afterloader is operated using the control console, which is placed away from the treatment location. The source location is displayed on the console in the course of treatment, accompanied by a print-out of the treatment plan. The treatment plan is transmitted to the control console by directly connecting the console to the treatment planning

computer, by means of a floppy disk, or by manual inputting of the data. The control console is easy to operate, and it contains a microprocessor that allows the automatic correction of the dwell times for decay.

The afterloader device is a mobile device with the requirement of a small floor room. The basic prerequisites for its design are: a protected container that shields the radiation emanating from the source when dormant or inactive; stepping motor; a source transferral and positioning feedback system; multiple channels for source transport; an indexer that automates the transfer of the source cable between the diverse transfer tubes, and transfer tubes that directly link the applicators to the afterloader device. In general, HDR applicators comprise thinner tubes. The connection of the applicator to transfer tubes and afterloader device forms a closed system that constantly thwarts the displacement of the source contained in the patient's body or prevents the source from dissipating into the air prior to getting to the target area. The three groups of applicators include intracavitary, intraluminal and interstitial. For intracavitary applicators, the specific transfer tubes are planned to have the similar total length with varying interlocks for all treatment channels to avoid inaccuracies in the connection. The HDR treatment employs an array of intracavitary applicators. A number of applicators are composed of durable stainless steel that is suitable for X-ray simulation, while others are composed of carbon fibre that are unable to generate artefacts on CT or MRI scans. The Intraluminal applicators are typically linked directly to the treatment unit by means of a specific adapter. These applicators can be blinded at each end, not reusable, and have flexible tubes. Interstitial applicators can either be flexible or inflexible (rigid). The length of the inflexible stainless steel needles can vary, hence the requirement for specific transfer tubes. Nonetheless, the needles remain usable following sterilization. To achieve standardized distribution of radiation dose, an implantation model with a fixed geometry is utilized. The constricted, elastic, non-reusable plastic tubes need various transfer tubes.

TPS is usually included in the system as a component in the afterloading treatment unit. After inputting the data, the dose is completely and rapidly calculated before being transferred to the treatment unit. A TPS basically consists of devices and procedures (a) an input device such as a digitizer that simulates the images or MRI/CT; (b) a password controlled source strength input; (c) 3-D geometrical reconstruction of sources and channels; (d) an algorithm that analyzes the placements of source dwell positions inside each channel; (e) graphic implant visualization in 2-D and elective 3-D; (f) calculation of dwell times; (g) a dose distribution algorithm; (h) potential for optimization; (i) computation of dose volume histograms (elective 3-D) and a plan for assessment parameters; (j) a documentation and visualization technique (e.g. printer); (k) a technique to transmit the treatment plan to the treatment unit. The conventional treatment process in a HDR-BT procedure is presented in Figure 1.

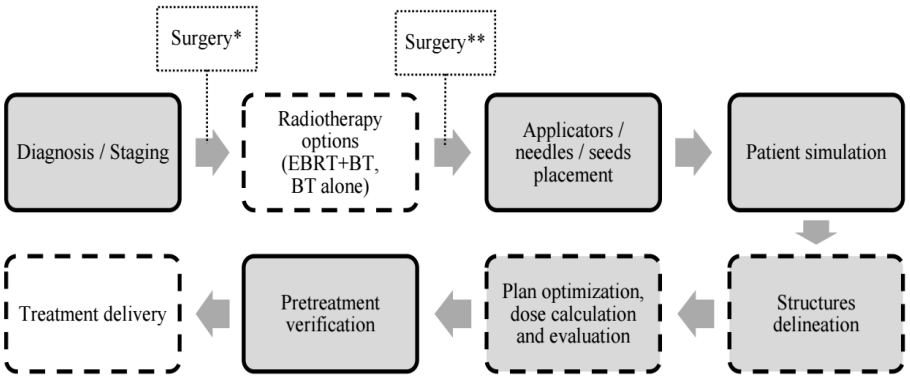

Figure 1: A typical treatment process in a contemporary HDR-BT procedure.

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4. Benefits of HDR-BT

HDR decreases the susceptibility of care givers and visitors to hazard associated with radiation exposure. This allows care givers to offer optimal patient care devoid of the trepidation related to radiation exposure. HDR further removes the provisions of source preparation and transportation, and facilitates shorter treatment durations. Given that there is a single source in HDR, the possibility of misplacing a radioactive source is negligible. There is less distress for the patient because lingering bed rest is removed. It improves the treatment potential for patients who are intolerant of lengthy bouts of seclusion, and persons at high risk of pulmonary embolism owing to protracted bed rest. Furthermore, there is less possibility of moving the applicator in the course of therapy. Also, the expenses of hospitalization are reduced given the accessibility of outpatient therapy provided by HDR. HDR increases the displacement of contiguous healthy tissues (through packing or withdrawal) which has the potential to decrease morbidity.

HDR-BT enables improved precision in the modifying the dose delivery to the level preferred by the radiation oncologist (Viswanathan et al., 2012). There is the possibility to attend to a huge volume of patients in places with a high number of brachytherapy patients but without adequate inpatient facilities. Nonetheless, HDR-BT enables intraoperative treatments that are done as the patient remains in the operating theatre. The diameter range of HDR sources is lesser compared to that of Cesium sources utilized for intracavitary LDR, which minimizes the need to dilate the cervix, thus decreasing the need to be heavily sedated or given general anesthesia. This allows the safe treatment of high-risk patients with low tolerance levels for general anesthesia. HDR provides possibilities for perivascular, endoluminal and transdermal insertions. HDR improves the possibility of optimizing dose distribution during treatment. Differences in the dwell times of a solitary stepping source permit a nearly unlimited disparity in strengths of the effective source, and positions of the source enable control of the dose distribution with the potential for lowered morbidity.

5. Delivery of radiation in HDR-BT

Dose delivery in brachytherapy is based on the inverse square law with swift decline in dose, resulting in negligible harm to the adjoining healthy tissue. The protected and uninterrupted delivery of radiation dose to tumor results in effective treatment outcomes, which are similar to those of other treatment modalities. Therefore, it is critical to ensure a rapid decline in the distribution of radiation dose close to the source and away from healthy tissue and OAR. The major steps in the delivery of radiation in HDR-BT include: in the case of prostate cancer, afterloading catheters are inserted into the prostate under the guidance of trans-rectal ultrasound (TRUS), followed by locking and stitching of the template to the perineum for CT planning, and then the acquisition of a CT image set and generation of a dosimetric plan. For treatment of the whole gland, 16 catheters are normally employed, comprising 12 catheters placed in the peripheral region, and 4 additional catheters that are centrally positioned. The arrangement of catheters is aimed at enabling good coverage of the prostate, while maintaining low dosage that reaches the urethral and rectal regions. Although the plan is typically to focus on the dominant nodule, one or two catheters can be added within the nodule to aid increase in dose. This rapid delivery of high radiation doses leads to radiobiological effects resembling that of extremely hypofractionated external beam radiation therapy (EBRT) that include stereotactic body radiotherapy (SBRT), and is considered to be selectively more destructive to cells with low α/β ratios. Radiation is delivered in HDR-BT by means of a high activity radioactive source that is coupled to a cable and moved along implanted catheters. The physical dimension of radiation source differs from 3.5 to 5 mm and 0.5 to 1 mm in length and diameter, respectively, conditional on the brand of equipment. Generally, step size ranges from 1 to 5 mm, although a step size of 2–3 mm is routinely utilized. The two most frequently employed sources are Iridium-192 and Cobalt-60, with photon energies of 380 keV and 1.17 - 1.33 MeV, respectively. Both HDR sources are capable of

generating comparable dose distributions inside the target volume. The source delivers radiation dose over its life span until it completely decays.

The source loading for HDR-BT is afterloading, where the applicator is initially emplaced inside the target volume, after which the radioactive sources are loaded, either manually by hand or done remotely. In HDR-BT, high radiation dose is able to be delivered to the tumor without impacting on the contiguous healthy tissues. Previously, afterloading involved the direct insertion of the radioactive material into the tumor, a process referred to as "hot" loading, thus exposing the oncologist and medical physicists to high radiation. Afterwards, manual afterloading techniques were developed to improve the delivery precision and decrease the potential radiation risk. This manual approach of afterloading entails inserting hollow-shaped needles, catheters or applicators into the tumor before being loaded with radioactive materials. With the advent of remotely controlled insertion of sources, the potential for radiation exposure to the oncologist, health workers, and visitors was minimized or eliminated. In the remote afterloading approach, the patient stays in a protected room while the treatment procedure is distantly controlled by the radiation therapist. Here, the afterloading involves first inserting the hollow applicators, catheters or needles into the tumor, and then connecting them by transfer tubes to the radioactive source that is kept in a protected safe inside the HDR afterloader. Afterwards, the radiation source is remotely controlled via the transfer tubes and then into the tumor.

The implant method was fully explained by Fukuda et al., (2014). Briefly, this technique entails the following key procedures: utilization of metallic applicators, constant delivery of epidural anesthesia, and performed under transrectal ultrasound (TRUS) guidance. For instance, in the case of prostate cancer, under real-time TRUS monitoring of the longest cross-section of the prostate, the applicators are inserted across the line that traverses the prostate (presence or absence of extracapsular invasion) as well as within the prostate with the exception of the urethra, at a spacing interval of 1- to 1.5-cm. For the rectal angle (posterior side), the applicators are positioned 0–3 mm within the prostatic capsule. The top 2 cm of the catheters pierce the prostate gland and then fixed inside the bladder.

6. Dose and fractionation for HDR boost

HDR-BT boost increases disease control rates for males with localized prostate cancer. Data strongly indicates that HDR-BT boost improves cancer control rates better than the implementation of EBRT alone, with no considerable rise in toxicity (Mendez & Morton, 2018). When utilized as a boost, the dose delivery of HDR-BT in prostate cancer is a high intraprostatic dose, which can be increased by the external beam component. The consensus guidelines outlined by the American Brachytherapy Society (ABS) for HDR prostate BT were not able to settle on a specific dose fractionation template for HDR boost, outlining high biochemical control rates in spite of a broad difference in dose and fractionation (Yamada et al., 2012). Guidelines from the European brachytherapy group, GEC/ESTRO reference the following HDR-BT schedules (Hoskin et al., 2013): 15 Gy in 3 fractions, 11–22 Gy in 2 fractions, and 12–15 Gy in 1 fraction. The HDR schedules were combined with the following EBRT dose fractionation schedules: 45 Gy in 25 fractions, 46 Gy in 23 fractions, 35.7 Gy in 13 fractions, and 37.5 Gy in 15 fractions over 5, 4.5, 3 and 3 weeks, respectively.

The selected dose and fractionation schedules were intended to be safe, effectual, and efficient to douse the early apprehension concerning safety of high dose per fraction. As more data emerged regarding dose and fractionation, regimens of 4 fractions of 3–4 Gy each that were earlier utilized increased to schedules that used a fewer numbers of larger fractions. For instance, Martinez et al., (2011) sequentially raised HDR dose from 3 fractions of 5.5 Gy to 2 fractions of 11.5 Gy, which was accompanied by an enhanced disease-free survival observed in patients undergoing treatment with two fractions of ≥9.5 Gy. Similarly, Morton et al., (2011) evaluated the hypofractionated regimen of solitary fraction of 15 Gy HDR combined with 37.5 Gy distributed in 15 fractions across 21 days.

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7. Dosimetry in HDR-BT

7.1 Dose calculation and dose points

An important step in HDR-BT treatment planning (TP) and delivery process is calculating the radiation dose delivered to the target volume. The dose calculation requires the dose-rate input, per second, from all dwell locations (Morén & Larsson, 2021). The dose calculations are normally done according to the American Association of Physicists in Medicine (AAPM) Task Group No. 43 (TG43) formalism (Perez-Calatayud et al., 2012), which considers the physiology of the patient is equivalent to water. In actual fact, this equivalence is unrealistic, but the water estimation of TG43 is normally assumed to be sufficiently adequate in certain cases, such as the HDR isotope ^{192}Ir. The first step entails the pre-calculation of distribution in the region of the solitary source, followed by scaling of the distribution with regards to the daily air kerma strength of the radiation source. Using the data derived from the calculation of source air kerma strength and the dwell times, the overall received dose at different points in the outlined features can be determined through the addition of the dose inputs from all dwell locations, which is the multiplication of dwell time by the dose-rate contribution scaled, with the radiation source strength. These dose points comprise discretized sections of the outlined features, and every dose point denotes a minute amount of tissue. Lahanas et al., (2000) developed a method to generate dose points.

7.2 Dosage verification for brachytherapy

Experimental dose have been verified using prototypes or commercial phantoms, and positioning appropriate dosimeters with the goal of measuring the dose distribution. The prototype phantoms typically mirror the human tissue and its heterogeneity, a critical component that is not considered by the commercially available phantoms (Jayakody et al., 2022). Several experimental approaches have been employed for the measurement of the dose distribution and heterogeneity/anisotropy functions of HDR sources. Dosage verification is carried out using radiochromic films, semiconductor diodes, metal oxide semiconductor field effect transistors (MOSFETS), ionization chamber, 2D ionization array (IA), scintillation detectors, flat panel detectors (FPDs), semiconductor detectors, thermoluminescent dosimeters (TLDs), optically stimulated luminescence dosimeters (OSLDs), gel dosimetry and Monte Carlo (MC) simulation (Palmer et al., 2012; Zhang et al., 2010). However, the inconvenient size of radiochromic film, scintillation detectors, and IC systems for real time dosimetry required the development of the more portable semiconductor detectors, gel dosimetry, and TLDs.

Film dosimetry provides 2D dose distribution for brachytherapy treatment verification. High spatial resolution, adaptability to the experimental design, modest energy dependency in a variety of beam properties, and tissue equivalency are the distinguishing advantages of this method (Sinnatamby et al., 2018; Jeang et al., 2018). The performance of radiochromic film has advanced in recent times, with the active layer being more homogeneous while the film now exhibits lower sensitivity to ambient light (Palmer et al., 2012). Gafchromic EBT2 radiochromic film was selected due to its comparatively higher resolution than other experimental techniques and higher validation than TLD outcomes, with a consistency in the ranges of 3.9% and 2.8% for dose rate constant and radial dose function, respectively (Uniyal et al., 2012). Subjecting the radiometric films to radiation causes the colour to change due to the polymerization process initiated by ionizing radiation. Either a spectrophotometer or a densitometer is typically utilized to measure the color enhancement of the film. These evaluations are articulated as rise in absorbance or usually referred to as optical density. Brown et al., (2012) demonstrated weak energy dependence of EBT3 film supports its suitability as a dosimeter in ^{192}Ir based brachytherapy studies. Several innovative dosimetric methods with GafChromic films were produced to evaluate the dose distribution in brachytherapy treatment in recent times

(Gholami et al., 2016). For instance, Gholami et al., (2016) employed film dosimetry to verify the dosage of the GYN brachytherapy treatment, and found that the observed dose distributions were compatible, both numerically and geographically, with the TPS isodose lines. The dosimetry equipment, however, could only measure discrepancies greater than 6%, according to the research. Moreover, Palmer et al. (2013) had previously shown that Gafchromic EBT3 film may be effectively used as a dosimetric approach for dose distribution assessment during HDR-BT therapy. Moreover, Asgharizadeh et al. (2015) showed greater dosage uniformity in the phantom where the EBT3 Gafchromic films were placed for a dosimetry system created for HDR rectal cancer brachytherapy treatment. Sinnatamby et al. (2018) verified that QA in HDR-BT may be used to mimic heterogenic structures using a stack of Gafchromic EBT2 films in a Poly Methyl Methacrylate (PMMA) phantom. In HDR 192Ir-BT dosage verification study, Oare et al. (2019) demonstrate the viability of using 3D printed PMMA and Acrylic Butadiene Styrene polymers instead of water.

Dosimetry in HDR-BT has also been verified using Ionization chamber (IC), which is regarded as a standard instrument that offers measurements of absolute radiation dose. IC measurements are dependent on dose rate , dose–response, attributes of the beam energy, quality of radiation, direction of radiation beam, stability of dosimeter under high temperature and humidity conditions (Stelljes et al., 2015). The requirements of ICs include adequate volume (≥250 cm^3) for sufficient sensitivity since low air kerma rate is utilized in brachytherapy. There are a variety of ICs for the verification of HDR dose (Yewondwossen, 2012; Poppe et al., 2013). Air-filled ICs as acknowledged as the typical detectors in brachytherapy dosimetry due to uncomplicated dosimetric characterization, reduction in the effects induced by recombination effects and durability. Nonetheless, this detector reportedly displays low spatial resolution due to their weak response in smaller active volumes. Austerlitz & Campos (2013) developed a cylindrical brachytherapy phantom composed of Solid WaterTM for the verification of radiation dose in HDR-BT TPS. MC simulation with the use of PENELOPE code prove the applicability of the phantom model for dose verification of HDR-BT treatment strategies as well as appropriateness for QA procedures at threshold levels of 3% and 2%, respectively.

MatriXX 2D ionization array (IA) is explored to analyze its feasibility for real-time dose verification in ^{192}Ir HDR-BT, particularly absolute and relative dose measurements (Yewondwossen, 2011; Zeman et al., 2012). Yewondwossen, (2011) developed a MatriXX 2D ionization array (IA) based on phantom prepared from a water-equivalent material, which significantly aided complete scattering states in the targeted area. In order to test the dose distributions for the ^{192}Ir HDR-BT source, the research demonstrated the validity of the MatriXX 2D IA. The feasibility of MatriXX 2D IA was also proven by Zeman et al., (2012), where a consistency of ±10% was found between TPS calculations and MatriXX measurements. Furthermore, Yoosuf et al., (2018) examined the HDR intracavitary GYN treatment plan using liquid-filled IC 2D array, positioned at 2 cm from the applicator plane, which demonstrated promising dose verification for HDR-BT treatment with higher sensitivity to positional error compared to air-filled 2D IC array and EBT3 Gafchromic films, possibly owing to their relatively high distinct resolution and self-attenuation features.

The utilization of scintillation detectors to verify doses in HDR-BT has been reported (Therriault-Proulx et al., 2011; Kertzscher & Beddar, 2017). The plastic scintillation detector (PSD) evaluated by Therriault-Proulx et al., (2011) displayed exceptional water-equivalence, linearity in response, high sensitivity, and resistance to radiation harm in addition to the capacity to eliminate stem effect using the chromatic removal technique. The major constraint of a scintillation detector is the phenomenon of stem effect light. Thus, this intrinsic properties of PSD support its suitability for real-time planned dose verification in prostate ^{192}Ir HDR-BT. On the other hand, Kertzscher & Beddar, (2017) reported that inorganic scintillation detectors (ISDs) are highly efficient, but possess a weak water equivalence; hence they are disregarded as viable dosimeters for dose verification. Nonetheless, ISDs prepared for a blend of YVO_4:Eu and Y_2O_3:Eu, which is a cost-effective approach and easy to fabricate and handle, are have a higher appropriateness for HDR-BT real-time verification.

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Flat-panel detectors (FPDs) are recently utilized as a diagnostic and radiotherapeutic tool for dosimetry verification in the course of HDR-BT treatment (Jayakody et al., 2022). For source tracking and pre-treatment imaging in ^{192}Ir HDR-BT therapy, a TPS based on FPD and a solid water phantom was created (Smith et al., 2016). To find radiation coming from the water phantom, the FPD was used. Similar to this, Nose et al. (2019) used an FPD system of the fluoroscopic X-ray device to verify the dosage in real-time for the sites of the HDR ^{192}Ir source throughout the course of treatment.. This verification approach allows for determination of the source location during the treatment program. FDP can also recognize deviations in HDR-BT treatment and guarantee safety of the patient. It was confirmed that this FPD dosimetric system offers precise dose verification, particularly under clinical settings.

Furthermore, semiconductor radiation detectors have been employed for real-time dosimetric verification, and have shown good consistency with film dosimetry and ICs in terms of spatial resolution and 2D dosimetry, respectively (Kertzscher et al., 2014; Carrara et al., 2018). For instance, metal-oxide-semiconductor field-effect transistor (MOSFET) dosimetry system exhibited percentage deviations of < 5% between the projected doses and the actual measured doses when used for dose verification of ^{192}Ir HDR-BT (Qi et al., 2007). In addition, Persson et al., (2018) reported dose comparisons of < 3% for the use of MOSFET detector for verification of the dosimetric precision of HDR-BT in a customized water phantom, although the response of MOSFETs is greatly dependent on the phantom size and spectrum of photon energies. Nonetheless, MOSFET detectors are constrained by the dependence on absorbed-dose energy, accumulated-dose and angular dependence, which results in wide-ranging characterization to reduce the ambiguities related to the detector's performance. These constraints can be resolved with the introduction ofdiamond detectors for semiconductor detector dosimetry studies. The benefits of diamond detectors include good stability, insignificant dependence on dose-rate, and homogeneous energy response in addition to low angular and temperature dependencies.

TLDs are extensively applied in brachytherapy because of their fairly smaller dimensions and high accuracy, and the equivalency of the average atomic numbers of TLDs and human tissues (Agostinelli et al., 2003). Given that TLDs are utilized to measure point doses for majority of the phantom studies (Lucas et al., 2012; Gambarini et al., 2012), It's possible that the measured dosage doesn't always represent the clinically meaningful dose that reaches OAR. One of the constraints of using TLDs as dosimeters is the requirement for repetitive measurements at different points (Jayakody et al., 2022). BR50/50™, Virtual Water™ (VM), aluminium and cork were employed to produce different designs of a heterogeneous phantom for the verification of TPS algorithms used in the HDR-BT (Moura et al., 2015). Dose distribution in the phantom was found to be consistent with the TPS calculations and simulations. The apparent disparity in the dose responses is attributable to the heterogeneous effect, which highlights the impact of heterogeneity on HDR TPS.

A procedure was developed, anchored in measurements in water/air using TLD-100H detectors, for the estimation of the spatial dose distribution in the proximity of a HDR ^{192}Ir BT source (Lucas et al., 2012). However, the effectiveness of TLD detector is constrained by its underestimation of the mean value close to the source (at approximately 1 cm) due to its dimension and high dose in the vicinity of the source. These limitations can be reduced by restricting positional differences in the locality of the HDR sources. Nikoofar et al., (2015) utilized TLDs to measure the dosage absorbed by phantom made from natural bone and mix of sodium chloride with paraffin wax. The TLDs measured dose at vital organs that include eyes and parotid, sub-mandibular, and thyroid glands, which exceeded the TPS dose distribution, whereas dose measurements by TLDs and TPS calculation for other organs like spine, trachea, and manubrium of sternum were similar. The effectiveness of TLDs as the dosimeter is based on its precision in vivo measurement device to assess dose delivery in HDR-BT systems and their ease of handling. The disparities between TLD measurements and TPS calculation are largely attributable to overlooking tissue heterogeneity in the TPS algorithm. Optically calculated luminescence dosimeters (OSLDs), which have a mechanism similar to that of TLDs, can also be applied in HDR-BT dosimetry verification. Silva et al., (2015) developed a sample phantom composed of

PMMA that showed higher accuracy in the assessment of the dose delivered to a bladder compared to radiochromic film in the course of GYN HDR-BT. OSLs can successfully serve the purpose of appropriately positioning the dosimeters, which is vital in the prediction of the adverse impact of the dose (Silva et al., 2015).

Polymer gels have the ability to study the dose distributions in the proximity of a HDR source, and a convenient tool for QA (Pappas et al., 2017). Gel dosimetry can be effective for dosimetry verification of radiotherapy, particularly in cases where conventional dosimeters are ineffective. It is capable of measuring intricate 3D dose distributions, precisely integrating dose regardless of dependence on the dose rate, in addition to high spatial resolution, tissue-equivalence, and absence of energy dependence across the bulk of the kV and megavoltage range. Moreover, Gel dosimetry is potentially capable of acquiring 3D dose distributions for HDR ^{192}Ir-BT sources (Senkesen et al., 2014). The performance of gel dosimeters for dose verification in brachytherapy has been attributed to its characteristic polymerization, oxidation-state change or color shifting attribute when ionized by radiation, capacity to permanently store data, and safe to prepare and handle (Watanabe et al., 2020). Fricke gel layer dosimeters (FGLDs) were reported to be a capable measurement tool for 3D dose distributions in HDR-BT. To compensate for theblurring of dose profiles near the brachytherapy source due to the diffusion Fe^{2+} and Fe^{3+} ions with the use of FGLDs, other polymer gels like nanoclay-based radio-fluorogenic gel (NC-RFG) and MAGIC gel were introduced in dosimetry studies. NC-RFG dosimeter may be used well as a quality assurance tool in HDR-BT, more effective than conventional gel dosimeters in areas of diffusion, hindrance of oxygen-induced reactions, and dose rate dependence, in addition to being more valuable in clinical practice due to its ability to easily obtain dose information within a short duration following the irradiation process (Watanabe et al., 2020). Watanabe et al., (2022) developed an MRI-based polymer gel dosimeter (PGD) as a 3D dosimeter to measure the intricate dose distribution in HDR-BRT. The PGD is a chemical dosimeter that is based on the irradiation-induced polymerization of H_2O radicals with vinyl monomers in the gel matrix. The PGD dose readout requires calibration information for the dose-transverse relaxation rate (R_2) response. Watanabe et al. evaluated the dose uncertainty and dosage resolution of three calibration techniques: the multi-sample and distance methods using the ^{192}Ir source, and the linear accelerator (linac) approach utilizing 6MV X-rays. With steep dose gradients, ^{192}Ir sources have been shown to enhance dosage uncertainty. The study found that the verification was an uncomplicated process of inserting the catheter/applicator into the PGDs, which makes them a functional verification tool for 3D dose distribution in HDR-BT with precise calibration techniques.

With regards to use of MC simulation to verify the calculated dose for brachytherapy dosimetry on patient anatomy and phantoms, a number of studies were performed (Teles et al., 2015; Pappas et al., 2017). MC is also utilized to evaluate clinically pertinent parameters, as well as the basic dose distribution close to the isolated HDR source (Sureka et al., 2006). The frequently utilized MC codes for brachytherapy dosimetry to construct the photon and electron brachytherapy source models followed by validation by means of various dose parameters based on the AAPM TG-43 protocol include MCPI, EGS, BRACHYDOSE, GEANT4, MCNP, TOPAS and Williamson's PTRAN (Faddegon et al., 2020). Sloboda et al., (2017) revealed that a thorough 3D model of a particular source configuration may be created utilizing dose estimations collected during brachytherapy treatment. This method mimics the dosimetric parameters particle fluence, air-kerma rate, and constant dosage rate at a geometric position.. Jayakody et al., (2022) outlined a synopsis of HDR-BT dose verification studies carried out using computational techniques. Based on the different dosimetric parameters, the MC codes: EGSnrc and EGS5 showed statistical errors of 0.2 and 0.7 respectively, for HDR-BT sources of MicroSelectron v2 ^{192}Ir and BEBIG ^{60}Co, Co0.A86. Other MC codes (PENELOPE, TOPAS, MCNPX, GEANT4.9.6, GEANT 4, PENELOPE 4 and MCNP 4) showed statistical errors of <0.5%. Chandola et al., (2020) comparatively analyzed the outcomes of MC codes (EGSnrc and GEANT4) in conjunction with validation by IC measurements, for the Nucletron mHDR-v2 ^{192}Ir-BT source. EGSnrc and GEANT4 displayed similar outcomes in TG-43 dosimetric data, with conformity of dose rate constant, radial dose function and 2D anisotropy function within 1%, within 2% up to 5 cm and within 6% up to 10 cm, and within 2% for polar angles $25° < \theta < 140°$, respectively. Lliso

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et al., (2011) effectively utilized GEANT4 for the determination of the electrons that were backscattered from the internal guard in HDR skin applicators. Benefits and constraints of various dosimetry methods are outlined in Table 1.

Table 1: Benefits and constraints of the various dosimetry techniques used in brachytherapy (Jayakody et al., 2022).

Dosimetric systems	Benefits	Constraints	Reference
Radiochromic film	Water equivalence; high spatial resolution; low cost of consumables	Need to characterize the film; requirement of scanners to obtain the dosimetric results	Sinnatamby et al., (2018); Jeang et al., (2018)
Ionization chamber (IC)	Capacity to be calibrated to achieve a closely absolute dose measurement	Requires voltage to operate, cannot be utilized in vivo as a result of finite dimensions; requires dose ionization conversion factors to be applicable	Poppe et al., (2013); Yoosuf et al., (2018); Stelljes et al., (2015)
Scintillator detectors	Plastic scintillator: small-volume dimensions, constant sensitivity; reproducibility; linearity of response; high level of water-equivalence; resistance to radiation harm; real-time operation. Inorganic scintillator: highly efficient	Plastic Scintillator: costly; stem effect; high predisposition to background light, hence background subtraction counter has to be applied that demands an additional set of fibers and PMT. Inorganic Scintillator: hindered by reduced water-equivalence	Kertzscher & Beddar (2017);
Semi-conductor detectors	High spatial resolution; high performance in 2D real time dosimetry; small dimension; capacity to combine with readout electronics.	Sensitive to variation in distance, not water equivalent	Qin et al., (2016); Boivin et al., (2015); Martinez et al., (2015)
Thermoluminescent dosimeters (TLD)	Small dimensions and obtainable in diverse forms; high accuracy; economical; re-usability	Requirement of annealing to remove the residual signal utilized for point dose measurements. Hence, there is the need for duplication and measurements at numerous points. Correction measures also need to be implemented, comprising those for energy, fading and dose response non-linearity	Nikoofar et al., (2015); Silva et al., (2015); Moura et al., (2015)

Gel dosimeters	Capacity to determine 3D dose distributions; tissue equivalence; can be shaped into any preferred form; displays proximate water equivalence; no required energy corrections for photon, and composed of electron beams to permanently store data; moderately safe to fabricate and handle.	Constant post-irradiation diffusion of ions, leading to the distortion of dose distribution	Papagiannis (2017); Watanabe et al., (2020); Maeyama et al., (2019); Vedelago et al., (2019)

7.3 Current dosimetry methods and Clinical outcomes of HDR-BT

Although HDR-BT is applicable in nearly all organs in the body, it is most typically utilized for the treatment of cancers of the lung, cervix, esophagus, and endometrium, while the head & neck, prostate, bile duct, brain, skin, breast, rectum, soft tissues and blood vessels have received relatively less attention from HDR. HDR-BT is commonly utilized as a module of multi-modality treatment that also comprises external beam radiation therapy (EBRT) and/or chemotherapy and surgery.

7.3.1 Cervical cancer

The utilization of HDR-BT for cervical cancer has considerably risen in the last decade in the U.S. and globally. Here, IC dosimeters and films are generally utilized to verify dose distribution, however they are constrained to point or 2D dose distribution assessments. HDR-BT demands the insertion of differently shaped catheter/applicator into the body for the aim of transporting the source to multiple positions, based on the geometries and positions of the tumor and normal tissue. Hence, 3D dose distribution verification is essential to compensate for the limitation associated with complex dose distribution of HDR-BT (Watanabe et al., 2022). This includes the combined use of 3D image-based dose-specification techniques and standard practice guidelines. In addition, the approach of interdigitating of The HDR-BT with EBRT may be employed to reduce the overall period of treatment, with EBRT usually delivered within the fraction range of 1.8-Gy to 45 Gy. Various organizations first administer considerable amounts of EBRT to reduce the volume of lingering disease, make certain that the lymph node regions of the pelvis are given 5 days of EBRT weekly providing it is possible to concurrently administer chemotherapy for at least 5 uninterrupted weeks, and enhance brachytherapy geometry since tumor reduction increases the space separating the tumor from OAR. Other institutions might chose to administer the initial brachytherapy fraction early on during EBRT with one fraction treatment weekly so as to curtail treatment period, although brachytherapy and EBRT are delivered on different days. In the case of large tumors, starting the therapy ahead of time and stipulating the dose to point A may lead to underdosing of the tumor volume resulting in poor localization of the delivered dosage. The ABS proposes the simultaneous utilization of cisplatin based chemotherapy for patients with sufficient renal functionality. In the course of weekly administration of cisplatin, the 5^{th} and 6^{th} doses of chemotherapy may be carried out in weeks when HDR-BT begins.

In the deployment of HDR-BT for cervical cancer, proper geometry of the implant is important irrespective of the simulation outcome or technique. The inaccurate positioning of the applicator will have detrimental effect on disease-free survival, thus raising the risk of local reemergence and frequent toxicity (Viswanathan et al., 2010).

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However, optimizing brachytherapy will not make up for poor positioning of applicator. Hence, TPS should be developed by a team consisting of radiation oncologist together with a competent physicist or proficient brachytherapy dosimetrist. Optimizing brachytherapy denotes the advanced procedure of attaining specific dose values at points or volumes inside the implant; rather than the basic development of a regular dose distribution that entails fixing dose points positioned in the region of the applicator. HDR-BT improves the precision in modifying the dose distribution to the levels recommended in radiation oncology. Organizations utilize either a squared or tapered distribution that conforms to the dimension of the cervix or advances into the uterus, respectively.

Attaining a satisfactory dose distribution with HDR-BT demands both accurate emplacement of the device and an effective optimization procedure. The challenge associated with 3D dosimetry involves harmonizing the dose distribution to the high-risk clinical target volume (HR-CTV) while concurrently circumventing the OAR. This challenge is complicated by the unknown dose delivered to the tumor, as specified by the HR-CTV, and raising the weight of a source drives the dose in every direction, to both the target and OAR.

Earlier studies (De Deene et al., 2001; Papagiannis et al., 2001) had evaluated the distribution of radiation dose in the proximity of the ^{192}Ir source by means of PGD, while Watanabe et al., (2019) performed measurements of dose distribution through the simulation of HDR interstitial brachytherapy. Watanabe et al., (2022) further conducted dose distribution measurement of a treatment strategy that simulated intraluminal HDR-BT for the treatment of cervical cancer via a VIPET gel dosimeter.The study proposed a technique to calibrate polymer gel dosimeters in medical stations to verify dose distribution for HDR-BT. This was followed by irradiation of the gel samples with 380 keV γ-rays of average energy emanating from the ^{192}Ir source and 6 MV X-rays from a linac. The gel was subsequently emplaced in a water-equivalent phantom to meet the requirements for backscattering. The treatment system consisted of a cylindrical glass container with dimensions of φ125 mm × 120 mm. A tandem and ellipsoidal shaped applicator manufactured with a glass tube is affixed to the glass container. Afterwards, a flexible catheter with a diameter of 2 mm attached to remote after-loading system (RALS) was put into the glass tube to translocate the source. A prescribed dose of 6 Gy was utilized.The distance, multi-sample and linac techniques were employed for the verification. The linac method decreased dose uncertainty and provided relatively higher dose resolution than the other methods. The linac technique also enhanced the dose uncertainty with increase in the slice thickness. Following the simulation of the clinical plan of a typical HDR-BT and the dose distribution verification for cervical cancer, VIPET gel dosimeters correlated linearly with doses in the range of 0–30 Gy, which covers the dose usually delivered in cervical cancer treatment. Georg et al., (2008) reported that HDR-BT is more effective than both IMRT and IMPT for cervical cancer. Gupta et al., (2021) evaluated the clinical results in patients with locally advanced squamous cell carcinoma of the cervix with limited residual disease at brachytherapy (BT) treated with high dose rate (CT)-based intracavitary BT (ICBT). For patients with limited remaining disease at BT, the treatment led to good local control and satisfactory toxicity.

There are external-beam radiation therapy (EBRT) and chemotherapy issues associated with HDR-BT. Viswanathan et al., (2012) reported that the combined treatment of EBRT and brachytherapy should have duration of <8 weeks, since improved control and survival of localized tumor can be anticipated with relatively short therapy. By interdigitating HDR-BT with EBRT, the treatment duration can be reduced, with EBRT typically specified in the range of 1.8-Gy to 45 Gy fractions. EBRT is usually administered as much as possible to reduce the amount of residual disease, making sure that 5 days of EBRT are delivered to lymph node regions of the pelvis weekly for as long as possible, chemotherapy is simultaneously administered for at least 5 consecutive weeks, and the geometry of brachytherapy has to be improved because of increase in the space separating the tumor and OAR as the tumor shrinks. As regards chemotherapy, ABS proposes the simultaneous utilization of cisplatin based chemotherapy for patients with sufficient renal functionality. In the course of the weekly administration of cisplatin, the 5th and 6th chemotherapy doses possibly coincide with when HDR-BT begins. Hence, the ABS suggests that chemotherapy may

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be deployed on the same day with EBRT rather than a brachytherapy day, by reason of the risk for more complications as a result of healthy tissue sensitization. Dose recommendation for HDR-BT in cervical cancer is dependent on the method adhered to for treatment strategy. The most frequently utilized dose regimens in the US are 45 Gy EBRT to the pelvis (probably accompanied with a sidewall boost), simultaneously subjecting the patients to cisplatin-based chemotherapy and either 5.5 Gy per fraction for 5 fractions (for patients who have exhibited either a total response or have <4 cm of remaining disease) or 6 Gy for 5 fractions (for patients with tumor size >4 cm following EBRT).The per-fraction dose delivered to the sidewall is most likely considerable, and thus patients with minute tumors or a total response with no pelvic-sidewall or lymph-node spread of disease do not need a sidewall boost while those with inflamed or engorged lymph nodes should be given a boost with EBRT. In recent times, the most regular HDR fraction size utilized in the US for all stages of cervix cancer is 6 Gy for 5 fractions, although issues were brought up regarding possible toxicity reaching the sigmoid colon and rectum in patients subjected to chemo-radiation (Forrest et al., 2010). Hence, current trials have expanded the dose range to 5.5 Gy for 5 fractions (Viswanathan et al., 2012). HDR interstitial BT may be delivered by doses outlined in Table 2. The equivalent doses of various HDR dose-fractionation regimes for cervical cancer are presented in Table 3.

Table 2: Doses for template-based HDR interstitial BT suggested by Viswanathan et al., (2012).

Dose of EB radiotherapy	Brachytherapy dose*	EQD2 (Gy) to CTV
45 Gy/25 fractions	3.5 Gy × 9	79.7
	4.25 Gy × 7	79.6
	5 Gy × 5	75.5
50.4 Gy Gy/28 fractions	3 Gy × 9	78.8
	4.5 Gy × 5	76.7

Table 3: The American Brachytherapy Society (ABS) suggested doses of EBRT and HDR-BT to be used in treating early and advanced cervical cancer.

Total EBRT Dose(Gy) @ 1.8 Gy/fx	# of HDR fractions	HDR dose/fx (Gy)	Equiv. Dose (Gy) for tumor effects	Equiv. Dose (Gy) for late effects with DMF = 0.6	Equiv. Dose (Gy) for late effects with DMF = 0.7	Equiv. Dose (Gy) for late effects with DMF = 0.9
Early cervical cancer						
19.8	6	7.5	85.1	59.5	71.0	98.0
19.8	7	6.5	82.0	56.7	67.1	91.5
19.8	8	6.0	83.5	57.0	67.4	91.6
45	5	6.0	84.3	67.0	73.4	88.6
45	6	5.3	84.8	66.8	73.1	87.7
Advanced cervical cancer						
45	5	6.5	88.9	70.1	77.6	95.0
45	6	5.8	90.1	70.3	77.6	94.7
50.4	4	7.0	89.2	72.6	79.4	95.3
50.4	5	6.0	89.6	72.1	78.6	93.7
50.4	6	5.3	90.1	72.0	78.3	92.9

7.3.2 HDR prostate BT

Mendez & Morton (2018) investigated the use of HDR-BT in the treatment of prostate cancer due to the susceptibility of this disease to radiation administered at high dose-rates or at high doses per fraction. This was done to make up for the issue of inadequate dosimetry that was brought on by LDR implantation due to seed loss or placement issues. As compared to low dose-rate (LDR) implants, HDR-BT provides quick delivery and high dosage conformality, which reduces toxicity. Patients with high and intermediate risks must have the combination of HDR-BT and EBRT because it results in a greater cancer control rate than using simply an external beam. For patients with intermediate or high risk, disease-free survival rates of >90% and 80% were obtained with a single 15 Gy HDR in conjunction with 40–50 Gy EBRT. For patients with low and low-intermediate risk, HDR monotherapy in two or more fractionations (e.g., 27 Gy in two fractions or 34.5 Gy in three) has shown to be a viable alternative to LDR-BT with less toxicity.

Zhang et al., (2020) built a HDR-BT program with real-time ultrasound-based planning for the treatment of prostate cancer. The program first started with subjecting the patients to injections of fluids to stimulate the emptying of their bowels (i.e. an enema) on the day of treatment procedure. Following the review of different HDR protocols, real-time ultrasound-based planning was selected in preference to a CT-based one (Batchelar et al., 2016; Morton, 2015). The HDR-BT operations were carried out while sedated with spinal anaesthetic. The whole surgery was overseen by an anesthesiologist. The patient was placed in the dorsal lithotomy position after the spinal anesthetic had been administered. Via the rectum, an ultrasonic probe attached to a stepper was inserted. Afterwards, a Foley catheter was inserted. The Foley catheter is loaded with aerated gel to improve picture quality when the urethra is not clearly delineated on the ultrasound image. After fastening a stiff template to the stepper, ultrasound pictures were taken. The prostate, urethra, and rectum were contoured after that using the photos that had been sent to the planning system. PTV was defined as a prostate with 3-mm margins on all sides, with the exception of the posterior area, which either had no margin or one if the attending physician deemed it necessary. A preplan was created using a standardized outline of catheter insertion and placement that was modified to account for the symmetrical, asymmetrical, or deviated architecture of each patient's prostate and urethra. After that, on the basis of the preplan, plastic afterloading catheters with a metal stylet were inserted within the prostate gland. The next step was to collect the second batch of ultrasound photographs. The placement of catheters was verified. The position of the validated catheter was then used to optimize the final treatment strategy. When transfer wires were connected to the HDR afterloader, the treatment delivery was carried out. All catheters were taken out after the procedure was finished. The patient was transferred to the recovery room after the Foley catheter was changed for a fresh one. The patients received a single dosage of intravenous antibiotics over the course of therapy. The Foley catheter and a three-day regimen of oral antibiotics were readied for release for the patients. The Foley catheter is scheduled to be taken out the next morning following the surgery.

As monotherapy and as a boost, HDR-BT treatment was deployed under radiation doses that were delivered in 2 fractions (1 week apart): 12.5 to 13.5 Gy per fraction and 9.5 to 10.5 Gy per fraction (Zhang et al., 2020). The external beam phase of treatment doses were varied from 46 to 50 Gy at 2 Gy per fraction. The pelvic nodal regions can be included based on the judgment of the treating radiation oncologist. The dosimetry and prostate-specific antigen (PSA) response of HDR were acquired and examined. Zhang et al., (2020) reported low occurrence of GU and GI complications in their cohort, which demonstrated that a HDR-BT program can be an effective option for the treatment of localized prostate cancer. As regards oncologic outcome, only a single patient succumbed to the metastatic disease after 1.6 years of treatment. The disease recurred in three patients (two prostate-only recurrence and one biochemical recurrence), but remained alive as at last follow-up (Median follow-up: 18.6 months, range: 3-55 months).

Hydrogel spacers (HS) have been used between the prostate and rectum in recent times as it is capable of safely and efficiently widen the peri-rectal distance separating the rectum from the prostate, hence reducing radiotherapy-related

toxicities. Chao et al., (2019) evaluated the utilization of hydrogel space (HS) in patients with intermediate- and high-risk prostate cancer subjected to combined HDR-BT and EBRT treatment, and its impact on prostate and normal tissue dosimetry as well as genitourinary (GU) and gastrointestinal (GI) toxicities. The initial HDR-BT was conducted 14 days before EBRT. Patients were positioned in the semi-lithotomy pose after being given spinal anesthesia. 3 gold fiducial markers were inserted into the prostate gland to enable image-guided radiation therapy (IGRT) for both HDR and EBRT. 14-18 HDR catheters were then transperineally inserted into the prostate by means of a template technique. Computed tomography (CT) simulation was carried out using a CT scanner with 1 mm slice thickness. This was accompanied by optimization of the treatment plans by utilizing the inverse planning simulated annealing technique. EBRT was started 14 days after deploying the HDR-BT. A CT simulation scan was repeated after removal of post-HDR catheter with 3 mm slice thickness. The GI and GU toxicities were evaluated. As reported, the insertion of HS significantly reduced the radiation dose delivered to the rectum, bringing about considerably low acute GI toxicity and a trend in the direction of reduced late GI toxicity.

7.3.3 Gynaecological cancers: Vagina andEndometrium

Grelewicz et al., (2017), Yildrim et al., (2019), and Cilla et al., (2020) carried out dosimetric comparisons for vaginal irradiation. For instance, Aydogan et al., (2006) investigated dose distributions of IMRT versus HDR-BT in the vagina in the course of post-operative irradiation of patients with early stage endometrial cancer. IMRT reduced the radiation dose delivered to rectum and bladder, with comparable target coverage and less heterogeneity, whereas HDR-BT displayed a lower integral dose. In the case of endometrum, Jones et al., (2014) analyzed the viability of stereotactic body radiotherapy (SBRT) and HDR-BT for dosimetric evaluation for early-stage endometrial cancer. HDR-BT demonstrated higher irradiation volume of the uterus with 150% isodose, although considerably higher target volume coverage was achieved with SBRT. In a case where pelvic EBRT is employed, the dose is typically 40-45 Gy in majority of treatments with midline shielding after around 40 Gy . A vaginal cylinder is commonly used to deliver HDR-BT. In addition, the dose delivered to the bladder was slightly higher for HDR-BT but lower for the rectum, sigmoid, bowels and femoral heads. The ABS outlines dose guidelines for only HDR or in tandem with EBRT for combination treatment of post-operative endometrial cancer. In combination with EBRT (0 – 45 Gy), ABS suggests HDR range of 4.0 to 10.5 doses per fraction (Gy) at specified points that include 0.5cm depth, vaginal surface

8. Image-guided HDR-BT

To achieve the reconstruction of source locations for dose calculation, 2D radiographs of the treatment spot are acquired including needles and applicators. The first step entails the calculation of doses at reference points based on the ICRU 38 recommendations for intracavitary BT. This approach offers a robust technique for positioning of an interactive applicator and reconstruction source position, but limited by the absence of the capability to visualize the anatomies of tumors and OAR, thus the need to incorporate 3D image-guided BT that comprises computed tomography (CT), magnetic resonance imaging (MRI) and ultrasonography (US) into HDR-BT. The 3D approaches provide 3D anatomical image datasets, which facilitates more precise patient-specific definitions of target volumes and OARs, as well as dosimetric assessment according to dose-volume relationships rather than point doses. Image-guided BT provides improved visualization of the tumor, and enhances the sculpting of the dose distribution due to better visualization of the tumor. This leads to improvement in clinical outcomes. Presently, CT is the most used IGBT modality due to its accessibility in radiation oncology clinics. The 3D imaging and image datasets (CT, MRI and/or US) has become a vital component of the general scheme of HDR process. Each imaging modality has its specific benefits for the enhancement of HDR-BT process. For example, transrectal US (TRUS) is interactively utilized to guide the insertion and arrangement of prostate implants. Based on its accessibility in majority of recent radiation oncology clinics, CT significantly enhanced the setting up and pretreatment verification of applicator and/or needles

in intracavitary and interstitial procedures (Castelnau-Marchand et al. 2016). MRI enhances the tissue contrast, which is a functional diagnostic and staging tool in the course of the insertion, planning and pretreatment assessment of a number of cancer types (Devic 2012, Damato and Viswanathan 2015, Castelnau-Marchand et al., 2016, Schmid et al., 2020).

Clinically, in radiation oncology, the procedure is conducted under image-guidance for the implantation of catheters or specific applicators into or close to the target location. Afterward, the patient is visualized by means of the selected imaging technique (CT, MR, and US) which is then transmitted to the planning software. This is followed by contouring of the target and OARs by radiation oncologists, while the medical physicist develops a treatment strategy. The key components of the BT delivery process involve defining the first "dwell" position and the precision/accuracy of the BT device (i.e. afterloader unit) by the medical physicist in order to perform accurate dwell locations and dwell times. Subsequently, the process of optimizing the dose is done to ensure the maximum potential dose is delivered to the tumor while constraining the dose that reaches the OARs. Following the assessment and authorization of treatment plan by the radiation oncologist, the therapist connects the catheters to the afterloader unit by means of transfer tubes. The treatment plan is executed under image-guidance and direction by all related personnel.

9. Clinical advances in HDR-BT

Aldelaijan et al., (2017) earlier performed experiments to study the effect of incomplete backscatter setting on the utilization of FF applicator for HDR-BT in the treatment of skin cancer. As reported, the dose variation between calculated and measured dose distributions was <3% (±4%) for treatment plans used of small lesions at depths of ≥2 cm. The measurement of absolute doses was done with the use of a reference EBT3 RCF dosimetry system within a Solid Water™ phantom at various depths relative to the phantom surface. In the case of larger lesions, a similar degree of dose variation was noted for depths of ≥1 cm. In addition, it was noted that supplementing smaller and larger targets with 2 cm and 1 cm slabs of bolus materials would reduce the dose difference to <3% (±4%) at both the surface and 0.5 cm beneath the surface, which is commonly utilized in the course of prescribing dose in patients undergoing treatment with FF applicator. Aldelaijan et al., (2020) developed an efficient technique for the accurate localization of the HDR source according to a measured 2D isodose map external to the source, derived from RCF dosimetry. Blob analysis was utilized for comparative analysis of the measurements of the relative isodose lines to a reference TG-43 library. The aim of the study was to enumerate and validate the dosimetric impact of the positional uncertainty of HDR source in brachytherapy by introducing a model for 3D position tracking of the HDR source anchored in a 2D measurement. The technique was able to optimize the precision of 3D source localization, and utilize RCF for the quantitative determination of the source location at a high accuracy (±0.1 mm). It is crucial to accurately localize HDR sources to develop an effective quality analysis (QA) technique for commercial and adapted applicators. In addition, this approach can be similarly expanded to other 2D imaging techniques.

An approach to enhancing the therapeutic ratio of HDR-BT, referred to as intraoperative HDR-BT, involves the delivery of irradiation in the course of surgery while the patient remains under anesthesia. This technique enables the retraction or shielding of radiosensitive healthy tissue in the course of surgery by limiting the radiation dose that reaches the healthy tissue (Nag & Scruggs, 2008). In addition, given that irradiation is delivered under direct visualization, the possibility of a geographic overlook is decreased. This supports the objective of achieving tumour debulking. The technique entails the irradiation of tumour bed by means of unique intraoperative applicators with parallel HDR catheters implanted in them, at a minimum separation of 1 cm. The utilization of a fixed geometry applicator enables the immediate treatment of the patient, with a preplanned library for the chosen applicator. Dose range of 10–20 Gy are typically delivered as a solitary fraction for duration of 10–60 min. Preferably, the surgery is conducted in a protected operating theatre with suitable imaging facilities and remote administration of anesthesia and a monitoring system (Nag & Scruggs, 2008). Due to the limited accessibility of completely operational and

protected operating rooms, only a few places carry out intraoperative HDR-BT. Several HDR equipment are approved mobile radioactive containers, which enable them to be jointly utilized by different hospitals particularly in cases where centers do not have adequate patient population to rationalize the acquisition of individual HDR equipment. Nonetheless, the progress in miniaturization of sources facilitates percutaneous interstitial BT via very thin 21 gauge needles, to specifically enhance the treatment of tumours that occur in the lips, eyelids and nose.

10. Conclusions

This article presents a detailed review of the verification methods for HDR-BT dose. Dose verification during HDR-BT aids optimization of the treatment plan. It reduces uncertainties and improves dose delivery optimization, which explains the considerable research work being undertaken in the area. Each verification approach has its benefits and constraints; hence the suitable method to adopt is dependent on a number of factors that include energies of the absorbed and accumulated doses, cost, position of HDR-BT source, susceptibility to background light, dimensions and resolution. By appropriately deploying well prepared experimental and MC dose verification systems, radiation doses delivered to the patient can be accurately estimated, thus determining the precise dose received by the patients devoid of mis-estimations. Nonetheless, there is need to develop advanced routine techniques to precisely determine the applicator position, target and OAR.

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