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Brachytherapy: A Comprehensive Review

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Brachytherapy, along with external beam radiation therapy (EBRT), is an essential and effective radiation treatment process. In brachytherapy, in contrast to EBRT, the radiation source is radioisotopes. Because these isotopes can be positioned inside or near the tumor, it is possible to protect other organs around the tumor while delivering an extremely high-dose of treatment to the tumor. Brachytherapy has a long history of more than 100 years. In the early 1900s, the radioisotopes used for brachytherapy were only radium or radon isotopes extracted from nature. Over time, however, various radioisotopes have been artificially produced. As radioisotopes have high radioactivity and miniature size, the application of brachytherapy has expanded to high-dose-rate brachytherapy. Recently, advanced treatment techniques used in EBRT, such as image guidance and intensity modulation techniques, have been applied to brachytherapy. Three-dimensional images, such as ultrasound, computed tomography, magnetic resonance imaging, and positron emission tomography are used for accurate delineation of treatment targets and normal organs. Intensity-modulated brachytherapy is anticipated to be performed in the near future, and it is anticipated that the treatment outcomes of applicable cancers will be greatly improved by this treatment's excellent dose delivery characteristics.

Keywords: Brachytherapy, Radioisotope, Three-dimensional imaging, Image guidance, Intensity modulation

Introduction

Presently, various types of radiation treatments are used to treat cancers. These include electromagnetic waves, e.g., gamma and X-rays, and particle radiation, such as electron, proton, carbon ion, and neutron beam treatment. Depending on the location of these radiation sources, radiation therapy is divided into external beam radiation therapy (EBRT) and brachytherapy. In brachytherapy, the radiation sources are temporarily or permanently placed inside or nearby the tumor. Most of the radiation sources used in brachytherapy are radiation isotopes that emit low-energy gamma rays. Hence, it has the advantage of deliver-

ing high-dose treatment to the tumor while also protecting the organs at risk (OAR) around the tumor. To deliver the dose to the tumor, brachytherapy applicators are required to move the radiation isotopes into the body. Various applicator types including interstitial needles have been developed and used to treat tumors; their designs are based on tumor type, location, and shape, as well as the treatment techniques involved, such as high-dose-rate (HDR) brachytherapy and low-dose-rate (LDR) brachytherapy. These applicators are typically used for the treatment of prostate, breast, gynecological, and skin cancers. Recently, various attempts have been made to implement the intensity modulation technique in the brachytherapy field, and

novel needles and applicators are being developed.

Another feature of modern brachytherapy is its integration with three-dimensional (3D) images, which are widely used in EBRT. Using a 3D image, it is possible to accurately delineate tumors and surrounding OARs and then prescribe the dose to the target volume while limiting the dose to OARs, compared with the point dose prescription used in two-dimensional (2D) treatment. Computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography-CT (PET-CT) can be used for this purpose. Particularly, MRI-based brachytherapy has been studied through extensive cooperation between Groupe Européen de Curiethérapie and the European Association for Radiation Therapy and Oncology (GEC-ESTRO) with the ultimate goal of achieving maximal tumor control and minimal radiation toxicity. A brief survey of the dose optimization algorithm to achieve this goal is also conducted in this review.

It is anticipated that intensity-modulated brachytherapy (IMBT) will be implemented in the near future using the aforementioned 3D images, a dose optimization algorithm, and novel applicators. Based on the excellent dose delivery characteristics of IMBT, it is expected that the treatment outcomes of prostate, breast, gynecological, and skin cancers will be greatly improved in the future. The current review primarily describes HDR brachytherapy.

Radiation Sources for Brachytherapy

The radiation sources used for brachytherapy must preferably be small enough to enable insertion into the body. Although these radiation sources also include extremely small electron guns in electronic brachytherapy that generate X-rays, isotopes are typically used for brachytherapy because they are easy to miniaturize. Radium was first discovered in 1889 and was initially used to treat skin cancers. In 1911, radium was temporarily administered through a urethral catheter for prostate cancer brachytherapy, and in 1917, transperineal implantation of radium was performed [1]. In the 1920s, patients began receiving radium brachytherapy in the United States. In the 1950s, Au-198 [2] was used for LDR brachytherapy, and, in the 1970s, I-125 seeds were used for prostate cancer implants [3]. In the 1980s,

the remote afterloading system was developed and used for HDR brachytherapy.

Presently, only one radionuclide, Ir-192, is used for HDR brachytherapy in the United States, whereas Co-60 is also used outside the United States. Two types of isotopes, Ir-192 and Co-60, are available in a single remote afterloading system. This approach has the advantage of reducing the treatment time and provides a better treatment plan than using a single Ir-192 source. However, it poses a new potential risk in the form of unintended source switching. There is also interest in using other radiation isotopes, such as Yb-169, Tm-170, and Co-57, as brachytherapy sources because they have long half-lives and low photon energy. However, compared with Ir-192 sources of the same size, these isotopes present other adverse issues in the form of low specific activity and low dose sensitivity to design tolerances [4].

Brachytherapy Applicators

Applicators used in brachytherapy have been developed in forms that are suitable for specific treatment sites. Interstitial (IS) needles are used to treat prostate cancers, whereas strut-adjusted volume implant (SAVI) applicators

Fig. 1. Brachytherapy applicators. (a) Henschke applicator. (b) Rotterdam applicator. (c) Fletcher applicator (tandem and ovoid). (d) Utrecht applicator. (e) Vienna applicator. (f) Venezia applicator. (g) Syed-Neblett interstitial template. (h) Miami applicator. (i) MUPIT applicator. (j) Intrauterine catheter and vaginal mold. (k) Interstitial needles. (l) SAVI applicator. MUPIT, Martinez universal perineal interstitial template; SAVI, strut-adjusted volume implant.

are used to treat breast cancers (Fig. 1k, l). Brachytherapy for cervical cancers is performed via intracavitary (IC), IS, or a combination of these two techniques, and the applicators corresponding to each technique are used. Particularly, IC brachytherapy treats tumors in the cervix and uterine cavity, and various applicators have been developed for this purpose (Fig. 1a-j).

The applicators available for the treatment of cervical cancers include the tandem and ovoid system (Fig. 1c, d), the tandem and ring system (Fig. 1e), the Henschke applicator (Fig. 1a), and an intrauterine catheter and custom vaginal mold (Fig. 1j) [5–9]. The applicators that can be used for the treatment of vaginal cancers include Rotterdam and Miami applicators (Fig. 1b, h) [10].

IS brachytherapy can use a classic Syed–Neblett parametrial butterfly template (Fig. 1g), a Martinez universal perineal IS template (Fig. 1i) applicator, or a Venezia applicator (an IC applicator used in combination with the IS technique; Fig. 1f) to achieve conformal dose distributions for bulky tumors, such as those with lateral parametrial expansion, extensive lateral pelvic wall involvement, and tumors with lower vaginal extension or that obstruct the os.

In the early 20th century, brachytherapy used a radium implant, and milligram time was used to prescribe the target dose. In 1938, Tod and Meredith [11] used “point A” to prescribe the dose, and the location of this point was determined using 2D images. However, because of the disadvantage that point A did not represent the entire tumor, the International Commission of Radiation Units and Measurements (ICRU; report 38, 1985) introduced a volumetric prescription for IC brachytherapy [12]. Additionally, the positions of the rectum and bladder among the OARs are described as representative points on a lateral radiograph. However, since the sigmoid colon and small intestine are not localized, it is difficult to assess their doses [12].

In IC brachytherapy, 3D images are used to determine both the location and the shape of a tumor and OARs. Conventional applicators for brachytherapy have been developed with the following two characteristics. First, CT/MRI compatibility and safety are guaranteed using titanium or plastic materials. Second, a combination of IC/IS systems, such as Vienna and Utrecht applicators, are used to achieve dose optimization for tumors with large and complex anat-

omies [13,14]. The selection of the key applicators used for implementing brachytherapy is summarized in Fig. 1.

Imaging for Brachytherapy

1. Two-dimensional image-based brachytherapy

In conventional brachytherapy, tandem and ovoid applicators are used together, and the appropriate position of the applicator is confirmed via 2D imaging, e.g., orthogonal radiographs. On the basis of these images, the pathways of a radiation source can be reconstructed and the radiation dose can be prescribed. These 2D images can be obtained using an imaging device, e.g., a C-arm X-ray machine.

2. Three-dimensional image-based brachytherapy

1) Computed tomography-based brachytherapy

A CT scan can visualize the tumor and OARs around the cervix in three dimensions and establish a 3D treatment plan accordingly. Such a CT-based treatment plan has the advantage of accurate dose evaluation because it is based on the volumes of anatomic structures rather than representative points [15]. According to early studies that included 3D plans, the estimated maximum doses to the rectum, bladder, and bladder neck, based on CT-based treatment plans, were higher than those estimated from 2D orthogonal images [16–21]. The estimated doses can vary significantly between patients, depending on the tumor stage, the thickness of the rectovaginal and vesicovaginal septa, and ovoid or ring size, which can only be identified using 3D images [22].

Kapp et al. [18] compared the rectum and bladder doses in CT images with the values of 2D orthogonal images in Ir-192 HDR brachytherapy of 720 cervical cases. They reported that rectum and bladder doses were, respectively, 1.37 and 1.44 times higher on average in CT-based plans. Additionally, they emphasized the need to evaluate the volumetric doses of OARs rather than the maximum point doses. Schoeppe et al. [20] and Datta et al. [23] compared rectum and bladder point doses on 2D orthogonal images with doses derived from CT. They found that the point doses on the orthogonal images significantly underesti-

mated the actual doses. Both studies also found that the point A dose did not adequately cover the target volume in all patients [20,23]. Consequently, point A doses, as well as the rectum and bladder points on 2D images, were poorly correlated with those of CT images.

Kang et al. [24] evaluated the clinical outcome of local control (LC) and late rectal bleeding for patients treated with a 2D or 3D image-based brachytherapy plan. The 3D treatment plans were adjusted by concurrently considering target volume coverage and OAR protection. Although the overall rectal bleeding rate was similar for both brachytherapy plans, the rate of severe rectal bleeding was significantly lower in patients using CT-based brachytherapy. The LC for patients with large tumors (>4 cm) was improved in patients using CT-based brachytherapy. Using one of three therapies, such as brachytherapy+surgery, EBRT+chemotherapy+brachytherapy+surgery, and EBRT+chemotherapy+brachytherapy, 98% LC could be obtained. Moreover, patients who received CT-based brachytherapy had significantly lower grade 3 or 4 gastrointestinal and genitourinary toxicity incidence rates compared with 2D image-based brachytherapy and had an improved survival rate without local recurrence [25]. Hence, CT-based brachytherapy appears to improve LC and reduce serious toxicity compared with 2D image-based brachytherapy because it can maximize the target coverage and minimize the doses to OARs.

2) Magnetic resonance imaging-based brachytherapy

Based on excellent tissue contrast, MRI-based brachytherapy is increasing. This approach enables delineating the gross tumor volume and clinical target volume (CTV), as well as the volume for OARs. Thus, MRI of CTV and surrounding OARs enables decreasing doses to the OARs and, accordingly, their radiation toxicity. This also means that if the dose constraints of all OARs are sufficiently satisfied, the dose to CTV can be increased. This dose escalation to CTV will lead to higher local tumor control.

Compared with CT images, MRI has the advantage of visualizing soft-tissue much better, thereby enabling the tumor and CTV to be accurately drawn. As such, MRI-based brachytherapy can adjust the dose distribution to achieve the prescribed dose. However, MRI-based brachytherapy includes several disadvantages, such as high equipment

cost, limited availability, limited applicator compatibility with this type of imaging, transferring an applicator-inserted patient for MRI, and a lack of understanding regarding MRI.

Dose Optimization

Most optimization methods developed before 2000 are based on the principle of forward planning. The dwell time of a radiation source is repeatedly adjusted to obtain a dose distribution that satisfies specific criteria using a conventional method. This method does not consider the presence of OARs in the optimization process but aims only to provide a uniform dose to the target volume [26].

Geometric optimization to adjust the treatment plans for breast cancer patients was reported by Anacak et al. [27]. In this study, only information about the catheter location was used. In another study for prostate cancer cases [28], the prostate and urethra, as well as the catheter, were displayed on CT images. However, this additional information was not considered during the dose optimization procedure. Since both of the above studies only used an approximation of the treatment target shape, the geometric visualization of the target did not guarantee that the actual target received a prescribed dose or that normal tissue did not receive an excessive dose. Therefore, the dwell times should be manually adjusted. Once the dwell times are changed, the dose distribution is recalculated and evaluated until the dose constraints are satisfied. This trial-and-error method takes a long time and has drawbacks, i.e., it is highly dependent on the experience of medical physicists [29].

According to studies reported since 2000, unlike conventional algorithms, some algorithms perform dose optimization by starting from the desired dose distribution. The objective of the treatment plan is defined by prescribing the dose constraints on the treatment target and OARs before optimization, and the patient's anatomy is considered in the optimization process. Finally, the result of this dose optimization is given by a set of dwell times for each dwell position. Based on this feature of the optimization process, this approach is referred to as inverse planning [26].

HDR treatment planning uses several mathematical

techniques to optimize the dose distribution, and these treatment planning methods are divided into heuristic and exact methods. The heuristic methods do not provide an optimal solution to a dose optimization problem but present a result close to the optimal solution within a reasonable time [30]. Thus, heuristic methods are more suitable for solving real problems. These heuristic methods are divided into stochastic and deterministic heuristic methods.

Stochastic heuristics search for an optimal value with a probabilistic property and converge it with a global optimum. Generally, this requires longer computing times compared with deterministic heuristics [31]. Particularly, simulated annealing is one heuristic method and a technology approach that many studies have adopted [32]. Lessard and Pouliot [33] developed the inverse planning simulated annealing (IPSA) algorithm, the objective function of which is to find a cost function that is associated with the dose objectives for the target and OARs. Before starting the optimization, the upper and lower limits of the acceptable doses in the dose points for the target and each OAR should be specified. The weights of the amounts exceeding these limits act as their importance in the treatment plan.

In the optimization process, the initial dwell times are set to an arbitrary value, and the initial cost function is changed by randomly increasing or decreasing the dwell time by a random value in each iteration. A new set of dwell times that provides a lower cost function is accepted in the iteration process. Since a relatively higher cost function may only be accepted with a relatively lower probability, the escapement from the local minima would be possible. If the cost function does not change over multiple iterations, the optimization process will stop. Lessard et al. [34] were able to automatically select the source's dwell position and then determined the optimal dwell time to meet the dose constraints of the treatment target and OARs using patient CT images and IPSA.

The deterministic heuristics algorithm optimizes the weighted sum of the dose variance objectives for dose points in and on the treatment target [35,36]. The optimization is repeated several times with different weights each time. Since the objective function is convex within the solution space, the deterministic heuristic quickly converges to the global minimum.

Unlike heuristics, the exact method provides an optimal solution to the problem. Treatment planning problems based on this method are formulated as linear programming problems that can be accurately solved using this technique. That is, the objective function and constraints appear as a linear expression of variables that must be determined [37-40]. In HDR brachytherapy, the dose optimization problem is often faced with difficult constraints that must be satisfied. Here, these constraints are related to dwell time, dose, and volumetric dose. Because it may be difficult to find a global minimum when difficult constraints are applied, a treatment plan corresponding to a higher cost function is often selected (e.g., a heuristic method).

In geometric optimization, the dwell positions act as dose points [41,42]. The dwell time at one dwell position is inversely proportional to the sum of the inverse squares of the distances to the other dwell positions. This sum is an approximation of the dose contribution of other dwell positions. When the source dwell positions in the same catheter are considered, geometric distance optimization must be effected. Conversely, when the source dwell positions are not considered, the geometric optimization of volume must be effected [41].

Graphic optimization is a convenient optimization method that has recently been widely used. In treatment planning systems that use this approach, the isodose lines of the brachytherapy plan are manually changed using a computer mouse. Manual adjustment of the isodose lines will instruct the algorithm to calculate the optimal dwell times. Tanderup et al. [43] compared the results of graphic optimization with those of geometric optimization and concluded that the former had better reproducibility compared with the latter.

Treatment Quality Management

Maintaining the safety and quality of brachytherapy has been comprehensively addressed in a series of reports by the American Association of Physicists in Medicine and other organizations. Specifically, the safety and quality of HDR brachytherapy are highly dependent on the procedural protocols of the activities performed by the medical

physicist and coordination among the brachytherapy team. The TG-59 report provides a list of items to be checked at each stage of treatment and additional information for quality control as a form of guidance. These documents can be useful tools for maintaining treatment quality and preventing errors [44]. The American Brachytherapy Society (ABS) also provides checklists for various HDR brachytherapy procedures for the same purpose.

Table 1 summarizes the examples of common failures occurring by treatment type. These failures are primarily caused by a lack of staff who fully understand the risks of brachytherapy treatment or its correct procedures. Thus, the HDR brachytherapy team requires skilled members who can perform their roles safely and correctly. Each treatment unit needs 0.4 and 0.03 full-time equivalent (FTE) staff who have a license for medical physicist and dosimetrist, respectively. In addition, 0.008 and 0.003 FTE staff per patient are also needed [45]. Thus, for a gynecological department with one HDR brachytherapy unit treating 100 patients each year, 1.2 and 0.33 FTE medical physicists and dosimetrists are needed, respectively.

Table 1. Examples of brachytherapy failures

Treatment site	Failure of brachytherapy
Prostate	Needles shifting from their intended position Inappropriate dose optimization
Breast	Length failures, either by erroneous measurement or entry (most common failure) Intracavitary balloons leaking or popping Intracavitary applicator rotating from the intended orientation
Gynecology	Incorrect length for 1 or more parts of the applicator Wrong dose specification location; for example, on a cylinder surface or at 0.5 cm away Wrong dose or dose combination with EBRT Applicator slippage between treatment planning and treatment delivery
Intraluminal	Incorrectly defining starting location for the source Catheter shifting from its intended position

EBRT, external beam radiation therapy.

Treatment Techniques

Brachytherapy techniques can be classified in terms of radiation exposure time, radiation source positioning relative to the tumor, and dose rate [46]. First, from a radiation exposure time perspective, there are two different types of brachytherapy, i.e., permanent and temporary. In the former, the radioactive sources permanently remain inside the body; in the latter, the radioactive source is inserted into a tumor or nearby it, and subsequently removed. Second, from a radioisotope positioning perspective, there is IS and contact brachytherapy. In the former, radioactive sources are positioned inside the tumor; in the latter (also known as plesio-brachytherapy), single or multiple radioactive sources are placed near the tumor. This contact brachytherapy is divided into four different types, i.e., IC, intraluminal, endovascular, and surface brachytherapy. Third, from a dose rate perspective, there are LDR (0.4–2.0 Gy/h), pulsed-dose-rate (PDR, 0.5–1.0 Gy/h), medium-dose-rate (MDR, 2–12 Gy/h), HDR (>12 Gy/h), and ultra-LDR (permanent implants, 0.01–0.3 Gy/h) brachytherapy techniques.

For HDR brachytherapy, particularly, appropriate applicators are placed in or adjacent to the tumor, which is temporarily exposed to HDR radiation. Radioactive sources are loaded on the applicators by a remote afterloading system. The iridium-192 isotope is typically used as a radiation source. To deliver the exact radiation dose to the tumor, the source should remain accurately at the dwell positions for the dwell times determined by the treatment plan. The doses delivered to surrounding OARs can be minimized through precise source positioning control and the rapid transit of dwell positions. After treatment, the applicators are removed from the patient's body [47].

Other common brachytherapy techniques include LDR and PDR brachytherapy. Comparing the treatment time of each technique, in the LDR approach, the radiation source is implanted for several days or permanently [48]; in the PDR approach, it is administered in pulses over several days [49], whereas in HDR, the treatment takes only a few minutes per fraction.

The most common brachytherapy technique is HDR, which is used as either a mono or boost therapy after EBRT.

HDR brachytherapy can be applied to prostate, breast, cervix, bronchus, esophagus, and lung cancers [50]. This approach has some advantages compared with LDR brachytherapy that includes a dosimetric benefit; because of the stepping source, medical staff can avoid radiation exposure because only one radiation source is used, and the patient does not need to be isolated for multiple treatment sessions [51].

The traditional problem with radiation therapy is that it kills cancer and healthy cells. Therefore, developing a precise treatment plan and delivering an accurate dose individually to each patient is very important to ensure successful treatment outcomes. Dose distribution in the patient is calculated by a computer system that takes into account patient anatomy, tumors, and critical organs and their dose tolerance. Quantitative models implemented in HDR treatment planning systems make an effort to optimize the dose distribution. As such, this planning issue can be expressed as a mathematical optimization problem. More specifically, it is a combined optimization problem that aims to establish an optimal dwell time combination. Varying the dwell time across the applicator can provide more radiation to certain areas than others. However, an increase in tumor dose can lead to an increase in OAR dose; therefore, this approach should be carefully considered [52].

The applicators (or catheters) and patient anatomy are image-mapped before a treatment plan is created. The structures of interest (including target volume and OARs) are drawn on the patient's image. The target volume comprises the tumor mass, which is typically expanded by a margin of 1 to 2 cm to include the microscopic tumor

extension. The OARs are located adjacent to the treatment target and may be exposed to a high (close to the prescription) dose. Dose points can be created in line with the target volume and, subsequently, be prescribed the desired dose. The actual dose at the dose point is equal to the sum of the dose contribution at each dwell position [53]. Optimization algorithms can be used to obtain the desired dose distribution. During the past 30 years, several studies on dose optimization using HDR brachytherapy have been conducted. Several quantitative models have been developed to address this planned optimization problem. These models use a unique method of minimizing the difference between the desired and the actual dose in the target volume and the OARs.

Presently, several research groups are developing IMBT techniques to deliver asymmetric dose distributions to tumors in, e.g., the prostate, breasts, cervix, and rectum. The techniques can be categorized into two groups, i.e., static and dynamic groups. The former technique includes static-shielded sources and static-shielded applicators [54]. Static-shielded sources emit low-energy photons from I-125 or Pd-103 isotopes and are used as LDR implants for breast and prostate cancers, ocular melanoma, and intraoperative brachytherapy for pancreatic and colorectal cancers. Eye plaque and a CivaSheet are examples of static-shielded sources [55,56]. Static-shielded applicators use Co-60, Yb-169, or Ir-192 isotopes; examples of these applicators include the Henschke ovoid, IC mold, D-shaped, Leipzig, and Papillon applicators [57-61].

The dynamic technique includes dynamic-shielded sources and dynamic-shielded applicators. The former applies Sr/Y-90 or Gd-153 isotopes; examples include

Fig. 2. Example of the dynamically shielded applicators for intensity-modulated brachytherapy.

partially shielded source and nitinol IS needles [62,63]. The dynamic-shielded applicators typically employ Ir-192 or an electronic brachytherapy source and a rotatable shield to limit and change the direction of radiation emission. Dynamic-shielded applicators are used for dynamic-modulated brachytherapy, single-shield rotating-shield brachytherapy (RSBT), dynamic RSBT, paddle-based RSBT, and multi-helix RSBT [64-67]. Fig. 2 shows an example of dynamic-shielded applicators for the IMBT technique.

To implement the above IMBT techniques, it is also necessary to develop a dose optimization algorithm for use in inverse treatment planning [68-70]. When developing the algorithm, dose delivery time and conformal dose distribution should be considered [71].

Treatment Sites

1. Prostate cancer

Brachytherapy of prostate cancers generally involves permanent seed implantation or HDR brachytherapy to the prostate. The 10 year survival rate was similar to that of radical prostatectomy, and there were fewer side effects (e.g., erectile dysfunction and urinary incontinence) [72]. Therefore, brachytherapy is one of the most effective and efficient methods for managing prostate cancer [73-76]. Brachytherapy can be used on its own for both primary and recurrent tumors and can also be used to escalate the tumor dose in combination with EBRT. Recently, it was used to treat the most patients with localized prostate cancer [77-82]. Prostate cancer brachytherapy can be performed using permanent seeds, such as in LDR treatment, or as a temporary management technique, e.g., in HDR treatment [83,84]. In both methods, the radioactive source is positioned inside the prostate gland. High-dose-ratio brachytherapy is performed with a removable catheter and radioactive sources such as Ir-192 and Co-60, whereas LDR brachytherapy is performed with a permanent seed, such as I-125, Pd-103, and Cs-131. Because the brachytherapy of prostate cancer concentrates the prescription dose on the tumor region, the fraction size can be increased higher than in the case of EBRT, and the treatment time can be significantly reduced. Since the end of the 20th century,

several societies have published several recommendations on brachytherapy for prostate cancer, which have come to represent guidelines for this particular treatment. Presently, brachytherapy is recommended as a monotherapy (without additional hormone therapy) for low-risk and intermediate-risk groups and as an accompaniment to EBRT in high-risk groups [85]. Brachytherapy is used more often for prostate cancer because it has a lower risk of potency disorders and dysuria. Additionally, this treatment is suitable for patients with other concomitant diseases or for patients who do not consent to surgery. Many men, for example, hope to be able to easily return to their daily and professional routines following treatment.

2. Breast cancer

Following a lumpectomy, traditional radiation therapy for early breast cancer lasts for 6 weeks. Such an extended period of daily treatment is extremely uncomfortable and may even be impossible for working women, elderly patients, and those who live far from treatment centers. Conversely, partial breast irradiation (PBI) or accelerated PBI (APBI) with brachytherapy, such as PDR for in patients or HDR for out-patients, can proceed within 5 days of treatment. Breast-conserving treatment (BCT) has been established as an effective therapeutic alternative to mastectomy for early breast cancer. The procedure comprises breast conservation surgery for tumor removal and EBRT of the entire breast and offers many advantages over a mastectomy. Along with excellent cosmetic results, breast cancer control rates ranging from 95% to 100% are indicated in almost all patients. Therefore, breast brachytherapy after a lumpectomy is a new treatment that provides equivalent LC, breast preservation, and improved treatment delivery [86-88]. Most women with breast cancer are good candidates for standard BCT and can be treated with lumpectomy and EBRT; however, only a small group of these women will be suitable candidates for breast brachytherapy. It is estimated that 71,000 women each year in the United States are eligible candidates for breast brachytherapy [89-91]. Brachytherapy is also often used as a boost to escalate the dose to the tumor bed or to treat local recurrence after mastectomy.

3. Gynecological cancer

Gynecological cancer encompasses cancers in the uterus, cervix, vagina, ovaries, fallopian tubes, and vulva. Brachytherapy is effective in the treatment of cervical cancer, endometrial cancer, vaginal, and vulvar cancer. It has been used to treat cervical cancer since the 1900s. According to US treatment data from 1973 and 1978, the 4 year in-field failure rate with IC brachytherapy and EBRT was 17% compared with without brachytherapy (47%, $P < 0.001$). Additionally, the 4 year survival rate was significantly improved to 70% for all stages compared with no brachytherapy (37%, $P < 0.001$) [92]. For cervical cancer, brachytherapy is superior to intensity-modulated radiation therapy (IMRT) because IMRT cannot achieve a target dose as high as image-guided brachytherapy (IGBT) while meeting the dose constraints (D_{1cc} and D_{2cc}) for the bladder, sigmoid, and rectum [93]. Moreover, cervical cancer brachytherapy has been further advanced with the help of CT or MRI.

According to the guidelines published by GEC-ESTRO in 2005 and 2016, treatment dose is prescribed to the target volume instead of using the point A approach [94-97]. In the same manner, the dose assessment for OARs is based on the dose-volume histogram instead of the reference points defined in ICRU 38 (Table 2) [98]. The guidelines of the GEC-ESTRO were further organized by ICRU 89 [99].

Table 2. Recommendation of dose constraints to targets and organs at risk in cervical brachytherapy

Target/organs	ABS	EMBRACE trial
Point A	Variable	No recommendation
HR-CTV D90	≥ 80 –90 Gy EQD2	According to institutional practice
IR-CTV D90	No recommendation	According to institutional practice
D_{2cc} bladder	≤ 90 Gy EQD2	< 90 Gy EQD2
D_{2cc} rectum	≤ 75 Gy EQD2	< 70 –75 Gy EQD2
D_{2cc} sigmoid	≤ 75 Gy EQD2	< 75 Gy EQD2

ABS, American Brachytherapy Society; EMBRACE, International Study on MRI-Guided Brachytherapy in Locally Advanced Cervical Cancer; HR-CTV D90, minimum dose to 90% of the high-risk clinical target volume; IR-CTV D90, minimum dose to 90% of the intermediate-risk clinical target volume; D_{2cc} , minimum dose to maximally irradiated 2 cc of the organ; EQD2, equivalent total dose in 2 Gy/day fractions, accounting for both the external beam and brachytherapy dose.

A comparative study of IGBT and conventional brachytherapy showed that IGBT reduced local recurrence, was more favorable for patient survival and toxicity [100,101], and was desirable as a standard treatment. Moreover, image-guided adaptive brachytherapy (IGABT) indicated improvement of the dosimetric and clinical results for definitive chemoradiation in inoperable cervical cancer [100,102]. The use of new IC/IS applicators (Fig. 1) and high-quality cross-sectional imaging are prerequisites for dose optimization.

According to the guidelines of the ABS published in 2012 [103,104], MRI has become the recommended standard modality for IGABT because of its high soft-tissue image quality. However, the high cost and complexity of MRI act as a major hurdle for its widespread use, particularly in developing countries with a higher incidence of cervical cancer. Consequently, the development of alternative imaging solutions for IGABT and the development of IMBT for dose optimization will have an important role in improving women's health worldwide. Besides the cancers listed above, brachytherapy may be effectively applied to head and neck tumors, skin, lung, esophageal, and bile duct cancers, as well as soft-tissue sarcomas.

Conclusions

In this review article, we briefly summarized the radiation sources, applicators, 3D images, dose optimization algorithms, treatment quality management, treatment techniques, and treatment sites relevant to brachytherapy. Brachytherapy, which has been developed for more than 100 years, currently has an opportunity to advance significantly as a result of EBRT techniques that have been introduced to the field. Particularly, 3D image-based brachytherapy using CT, MRI, and PET-CT has already been applied to patient treatment; the IMBT technique, which generates asymmetric dose distribution generated by a radiation shield or multiple source channels, is presently under development or already in use. The IMBT technique will not only deliver high radiation doses to tumors but will also help to protect OARs within tolerable dose levels. It is expected that the treatment outcomes of prostate, breast, gynecological, and skin cancers will be greatly improved in

the future as brachytherapy techniques become more advanced.

Conflicts of Interest

The authors have nothing to disclose.

Availability of Data and Materials

All relevant data are within the paper and its Supporting Information files.

Author Contributions

Conceptualization: Young Kyung Lim. Investigation: Dohyeon Kim. Writing – original draft: Young Kyung Lim and Dohyeon Kim. Writing – review & editing: Young Kyung Lim.

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