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Review Article

An Update on Brachytherapy for Cervical Cancer: A Review

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Abstract

Introduction: Cervical cancer remains one of the most common malignancies affecting women worldwide, with over 600,000 patients globally every year, and is a leading cause of cancer-related mortality in women. Although there have been advancements in both screening and prevention, radiation therapy, with or without chemotherapy, is the standard of care for treating locally advanced cervical cancer. Radiation typically consists of two methods, external beam radiation therapy (EBRT) and brachytherapy, which have both evolved in their own respective ways technologically and for patient accessibility. This article aims to review the different cervical cancer brachytherapy techniques, such as intracavitary and interstitial approaches, including their advantages and drawbacks.

Methods: Resources on PubMed between the years 2000 and 2024 were reviewed based on their relevance to the approaches of brachytherapy. Articles were found through the use of key terms and Boolean operators such as ("cervical cancer," AND "brachytherapy," OR "high dose rate brachytherapy,") OR ("intracavitary," OR "interstitial brachytherapy," OR "hybrid brachytherapy,").

Discussion: Three techniques of brachytherapy are de: intracavitary brachytherapy (ICBT), interstitial brachytherapy (ISBT), and hybrid intracavitary/interstitial brachytherapy (HBT).

Conclusion: Brachytherapy is a vital part of definitive cervical cancer treatment. While ICBT remains the standard of care for most cervical cancers, ISBT and HBT approaches remain important treatment options. HBT has been shown to address variances in patient anatomy and tumor geometry, resulting in better tumor dose coverage and improved outcomes through minimizing toxicity.

Introduction

Cervical cancer affects and kills hundreds of thousands of women pedecreased global rates in the past decades [1,2]. Radiation therapy, with or without chemotherapy, is considered the standard for locally advanced cervical cancer by the American Society for Radiation Oncology (ASTRO) [3]. Radiation therapy typically consists of external beam radiation therapy (EBRT) and brachytherapy [3]. EBRT, which uses high-energy particles, has included and evolved from two-dimensiononal plannng,its 3-dimensional conformal technique (3DCRT) or intensity modulated radiation therapy (IMRT) [4]. Similarly, brachytherapy has included and evolved from low dose rate (LDR) brachytherapy requiring inpatient admission, to High Dose Rate (HDR) brachytherapy, mainly an outpatient treatment [5,6]. Recently, HDR brachytherapy has included imaging for image-guided brachytherapy (IGBT), addressing the main shortcomings of older forms of brachytherapy [7,8]. Previous brachytherapy treatment used predetermined anatomical points to map out tumors, disregarding variances in patient anatomy and patients with abnormal or bulky; however, the developments and evolutions of brachytherapy have addressed these problems in a safe and effective approach [5,7,9].

The actual application of brachytherapy varies greatly throughout the world because of fluctuating technology access, lack of sufficient training, and varying knowledge of the new technologies [5,9]. This article aims to review the various cervical brachytherapy techniques, such as intracavitary and interstitial approaches, along with the advantages and shortcomings of each approach.

Methods

Prospective trials, guideline documents, retrospective studies, and review articles located on PubMed between the years 2000 and 2024 were reviewed. Articles were found through the use of key teand Boolean operators such as ("cervical cancer," AND "brachytherapy," OR "high dose rate brachytherapy,") OR ("intracavi," OR "interstitial brachytherapy," OR "hybrid brachytherapy,") Then the articles were chosen based on their relevance to the approaches of brachytherapy.

Discussion

Brachytherapy is typically included in the definitive treatment management for women with a FIGO staging of IB2 to IVA [2]. For example, women with a tumor that is in the pelvic region but extended past the cervix usually have a treatment plan that includes brachytherapy [2,6]. Brachytherapy should be performed if feasible, as Ebe an inferior treatment compared to EBRT and brachytherapy [10].

Brachytherapy uses a radioactive source that has the ability to converge on the tumor closely, allowing for a higher radiation dose due to the inverse square law [6]. The inverse square law shows a relationship whereas the distance to the source decreases, the intensity of radiation increases dramatically [6]. The ability to use a tumoricidal dose, which is greater than 80 Gy, makes brachytherapy effective in not just destroying gross tumors, but also protecting the nearby healthy cells and organs [6]. This ability cannot be said for other techniques, such as EBRT, stereotactic body radiation therapy (SBRT), and intensity modulated radiation therapy (IMRT), which cannot maintain a high dose and optimal target area concurrently [3,9]. This advantage is visualized in a worrying trend in patients who do not undergo brachytherapy: a review by Banerjee et al. details that reductions in cause-specific and overall survival within cervical cancerare indeed tied to a decreased usage of brachytherapy [6,11]. The EMBRACE I study, which is a large-scale study that implemented MRI-guided brachytherapy, noted that there was an actuarial five-year overall survival rate of 74% [7,12], thus affirming that without the use of brachytherapy in the treatment of patients with locally advanced cervical cancer,drop, emphasizing the therapy's importance.

The current globally accepted standard of care is definitive chemoradiation, which consists of brachytherapy with concurrent chemotherapy and EBRT [13]. EBRT is modeled to treat microscopic disease with a dose sufficient to cover the parametria, pelvic lymph nodes, and the primary tumor [6]. Unlike brachytherapy, the widespreaddspread of the radiation dose potentially limits cancer spread in areas that were subclinical and microscopic, such as the parametria and pelvic lymph nodes [2]. Despite this, the EBRT still fails to adequately descells and simultaneously avoid damage to nearby organs and tissues as a result of the larger volume of radiation through a less centralized area [6].

Evolution of brachytherapy techniques

Radiography was initially conducted on plan film X-rays, as well as many other 2D images [6]. Radiation doses were given from a reference point called "point A," which, according to Tod and Meredith's Manchester System, is the location 2 centimeters higher than the cervical opening and 2 centimeters lateral to said opening, along a plane perpendicular to the intrauterine tandem, or the radiation-delivering rod placed inside the radiation. Point A was used to estimate the area where the uterine artery crosses the ureter. This region is prone to both early and distantdtumor spread and radiation injury, per Tod and Meredith [7,14]. Additionally, Point A also shows a point of limiting tolerance, or the dose where the optimal tumor control and optimal radiation dose are present, such that surrounding structures are least likely to be impacted in a harmful manner [7,14]. Because this time period did not have 3D-guided therapy, using a Point A was typical for brachytherapy placement.

While 2D imaging was widespread during this time period, it had numerous constraints. One such limitation was the limited visibility of the surrounding areas of Point A, creating a visual map that didn't truly reflect reality due to its inability to create a reference-based location involving surrounding organs. This setback caused point A to often be far too deep inside the uterus, or outside the actual uterus, a consequence of the variety of individual patient anatomy. This weakness was noted by Potter et al. and Datta, et al. corrthe claim that due to the lack of consideration for a patient's individual anatomy, radiation doses were given at levels that harmed surrounding healthy organs [6,15,16].

As shown, 2D planning's fatal flaw was the inability to provide an image that provided mapping that accounted for the individual patient's anatomical differences; this problem was later addressed by 3D technologies [6,9]. For example, MRI and CT become integrated into the treatment paradigm, framing the way for other 3D imaging like 3D image-guided brachytherapy (IGBT) [9,17]. The usage of IGBT allowed us to realize that Point A was not an optimal point for brachytherapy because large tumors tended to overgrow the brachytherapy [7,18].

MRI became the 3D imaging modality of choice, leading to a plethora of radiation, including the High-Risk Clinical Target Volume (HR-CTV) [7,17]. The HR-CTV better defines individualized patient anatomies and provides a more accurate and larger high-dose radiation coverage, ensuring that, unlike the 2D imaging, brachytherapy at the correct location will not affect healthy surrounding organs. The EMBRACE I study found that MRI-guided brachytherapy created a 5-year local control of 92% in the FIGO stages IB-IIA, as well as 80% in FIGO stages IIB-IVA, when compared to controls involving the usage of 2D/Point-A based approaches [7,12]. This proves the superiority of volume-based planning in the context of finding optimal radiation doses.

Comparison of ICBT, ISBT, and HBT

Intracavitary Brachytherapy (ICBT): Brasmaller-sized chemotherapy IntracavitaryrBrasmaller-sized chemotherapyapysmaller-sizedcsmaller-sized tumors, especiallhosyounger individuals. More specifically, ICBT is used when the HR-CTV is less than 18.8 cm^3, when the position of the tumor is symmetrically distributed in relation to the uterine cavity, and without any invasion of the tumor into the parametrial tissue. ICBT is considered extremely important when reviewing various brachytherapy techniques in general [3].

For ICBT, using an applicator, a radioactive source is put through the vaginal cavity and next to the tumor [19]. This is frequently rodse using a tcurveddcurvedederodsodare inserted through the endometrial coval-like parts, are put laterally in the fornices of the vagina behind the cervix [6]. Because of the inverse square law (where the radiation dose decreases by the square of the distance), ICBT is able to provide a decently high dose of radiation for the tumor, while simultaneously leaving healthy organs relatively unharmed [6].

ICBT was historically done using a lower dose rate (LDR) for radiation, consequently leading to longer treatment times, including hospitalizations, and a higher risk of radiation risk for the healthcare personnel [6]. The uptick in high-dose rate (HDR) brachytherapy has caused an increase usage of iridium as the source of radiation to allow for more treatments [20]. Also, HDR utilizes a method called remote after loading technology, where the source is robotically driven through channels of an applicator to points created after 3D imaging [6]. This allowed for a more optimal personnel involvement, as staff no longer had to insert the source inside the patient [6,9,21].

ICBT is optimal when the tumor is symmetrically positioned in the uterus, within the uterus, and centrally located [5]. The advantages of ICBT include the ability to give high central doses of radiation and a non-invasive methodology, making ICBT effective. On the other hand, when dealing with nonideal tumors, such as asymmetrically positioned tumors, ICBT is not effective as a stand-alone treatment [5]. Yoshida, et al. conducted simulations that showed that largapproached with a combined approach, as using ICBT alone in this scenario may underdose the tumor or result in other negative effects [5,22,23].

Interstitial Brachytherapy (ISBT): Interstitial brachytherapy (ISBT), which is an advanced form of radiation therapy, is typically used when ICBT is utransperineal approach, ISBT uses a direct placement of or hollow tubes around or into the residual disease [6,24]. On the other hand, ICBT uses a noninvasive method in order to put a radioactive source inside the body's cavities through an applicator. Because ICBT's usage of an applicator that creates a more standard central placement, and the fact that the placement of ISBT is direct, ISBT allows for a more accurate insertion of radioactive sources near or into the tumor [6,24]. Additionally, due to the direct placement procedures in ISBT, interstitial brachytherapy tends to be done in an operating room with forms of sedation, including spinal/epidural and sedation and/or general anesthesia [25]. To ensure the precision of the placement of the catheters, techniques such as fluoroscopic, ultrasound, MRI, CT, and laparoscopic guidance are used. Even though the direct placement may seem tedious, it is extremely helpful for more personalized cases, including abnormal tumors, because of the flexibility with placement [6,24,25]. ISBT is often used in cases with lower vaginal involvement, large tumors, cases with patients without the ability to have fitting intracavitary applictionswho develin the cervical health, and lateral extension of the disease [5,25,26]. Pinn-Bingham reported that ISBT improves locoregional control rate, shown with data from his retrospective analysis in 2019 [27].

While ISBT provides a solution for abnormal cases and tumors of irregular shape, size, and irregularities, it lacks in central target dose coverage. This weakness was corroborated by Bansal, et al. who found that the average high-dose volumes in ICBT were much hthose of ISBT [28]. Additionally, ISBT requires strict conformance to precision [5,29,30]. Because of the advantages and disadvantages of ISBT, it is extremely important for the protection of the surrounding organs' health, and ISBT is frequently used for specialized cases.

Hybrid Intracavitary/Interstitial Brachytherapy (HBT): In recent years, brachytherapy has changed to better address abnormal and irregular tumors. Specifically, hybrid intracavitary/interstitial brachytherapy (HBT) has become a vital method for making up for the weakness of ICBT and ISBT: ICBT can give an inadequate dose coveracan underdose the areas in the central cervical region [5,7,31,32].

Pawho undergo HBT usually have large and/or abnormal tumors with remarkable qualities, such as a residual tumor larger than 4 cm post-EBRT or ones which had an initial diameter that is greater than 5 cm [9,33]. HBT therapy is for use with lower vaginal segment involvement, ill-fitting intracavitary applicators, cervical stump cancer, and incomplete target volume coverage [5,6,31,34]. Other indications of HBT include cases with a poor relative position between the organs at risk (OARs); hybrid techniques can use better dose sculpting, which can maintain a reasonable OAR dose and still increase tumor dose [5,6,19,35].

Because HBT is a combination of intracavitary and interstitial brachytherapy, the patient benefits from the advantage of both techniques. One such example is a decrease in required needles, which is elicited from using ISBT techniques [6]. The hybrid applicators involve placing the interstitial catheters through the vaginal cavity, rather than the perineum [31,32]. This approach allows for safer needle insertion as well as a much more precise dose delivery [6]. As ISBT requires advanced anesthesia techniques [24], HBT potentiallused in clinic, with oral anesthesia or moderate sedation [36,37].

There are various types of hybrid applicators: tandem and d-based, ta and cylinder-based [5]. The different hybrid applicators each have variations in their needles, including the orientations that create different dose coverages and the number of needle channels, known as the needle geometry [31,32,38,39]. Per the EMBRACE I study, a significant improvement of 14% in local control rate in patients in FIGO stage IIIB [7,12]. HBT has improved local control while limiting long-term side effects, making it suitable for usage in a case where intracavitary applicators are inapplicable [5]. See Table 1 for a summary.

Brachytherapy technique comparisons and considerations

The clinical efficacy of brachytherapy in cervical cancer has been examined through the lens of ISBT, ICBT, and HBT approaches. Each approach holds its own respective advantages and disadvantages in regard to toxicity, survival, and local control. Brachytherapy can enable a highly conformal tumor "boost" when combined with concurrent chemotherapy and EBRT, all while minimizing radiation dose to OARs like the rectum and bladder from harmful side effects [6].

ICBT is to be one of the most effective forms of brachytherapy, as a result of the easy application and non-invasiveness [5]. For most typical or freshly developed cases where tumors are symmetrical and without parametrial tissue invasion, ICBT has been noted to cause local control rates of 75% - 95%, showing the success of ICBT in these kinds of cases [5,32]. When faced with irregular tumors that do not fit normal profiles or locally advanced cervical cancer, ICBT becomes less useful, with LC rates of 45-80% [40]. Because of the symmetrical dose distribution in ICBT, abnormal and asymmetric tumors that do not adhere to norms are notfor ICBT. For this reason, asymmetrical and irregular tumors tend to be met with a different approach than ICBT [5,41].

One such approach to brachytherapy is ISBT. In ISBT, catheters are placed using a vaginal and/or transperineal approach [6,42,43]. ISBT is quite invasive, requiring higher anesthesia and technical expertise, along with carrying a higher incidence of bleeding complications, such as perforation, bleeding, and tumor underdosing [5,29,44]. While these negatives are present, ISBT does a superb job in locoregional contof abnormal, larger tumors [5,35,45]. Still, ISBT's resource and knowledge needs, along with weaknesses in central cervix sage,cause its utilization to be limited [5,30].

HBT is another major approach to brachytherapy that combines the best features of ISBT and ICBT: lateral reach and central dosimetry, along with potentially less anesthesia and resource needs [19,36,37]. This allows for a personalized dose escalation, helping treatment plans account for individual situations and anatomies [19]. The HBT techniques use 3D imaging for planning in order to better map out the treatment plan, which, combined with the interstitial needle placallows for optimal tumor coverage [8]. The HBT technique has been described as the most "flexible brachytherapy, and can be used for the widest variety of clinical scenarios" [6,12]. A combined use of IGBT usian reflects the most versatile and thorough brachytherapy strategy by maximizing locoregional control and minimizing toxicities [6].

Implementation, considerations, challenges, and resource limitation

It is important to consider the tecskills and resources that many centers have. Many centers do not have the personnel or the adequate training to conduct complex brachytherapy processes, especially the logistics and operator training

Table 1: Comparison of ICBT, ISBT, and HBT.

	Indications	Procedure details
Intracavitary Brachytherapy (ICBT)	Smaller tumors Symmetrical tumors No parametrial invasion Minimal vaginal involvement [41]	Intravaginal placement In the office, procedure room, or operating room General anesthesia, minimal to deep sedation [5]
Interstitial brachytherapy (ISBT)	Larger tumors Asymmetrical/Irregular tumors Parametrial involvement, to the sidewall Any vaginal involvement Cervical stump tumors [5,35,45]	Vaginal and perineal placement of needles Typically, in the operating room, with general, spinal, or epidural anesthesia Possible hospital admission depending on fractionation [25]
hybrid intracavitary/ interstitial brachytherapy (HBT)	Large tumors Asymmetrical/Irregular tumors Parametrial involvement, not to the sidewall Minimal vaginal involvement Cervical stump tumors [19]	Intravaginal placement In office, procedure room or operating room General anesthesia, minimal to deep sedation Potentially vaginal bleeding on removal (19, 36, 37)

that is required [5] Resource and personnel scarcities is a significant barrier to widespread implementation of hybrid procedures, as detailed by Banerjee and Kamrava concur that there are limited centers with sufficient prowess in interstitial brachytherapy, and implementation of this training will take a long learning period [6,7]. Personnel shortages are becoming even more apparent when we consider that ISBT and potentially HBT practices usually involve sedation/ anesthesia, requiring another group of specialized individuals. This can create a significant barrier for many centers, as the importance of anesthesia and resourcesis heighteto implementing brachytherapy approaches like the ISBT or HBT approach.

There have been theorized replacement approaches, but many of them also introduced their own shortcomings. For example, IMRT and ICBT can potentially be a viable solution after EBRT [5]. While after EBRT, ICBT and IMRT can serve as an alternative to ISBT or HBT approaches, IMRT has a higher toxicity potential noted in clinical case; it is not likely to be implemented as a viable substitute [5,46,47]. Another such limited approach in low-resource centers is HDR brachytherapy, due to the fluctuating capabilities and clinical workflow of the center [6,20]. HDR brachytherapy uses an Iridium for the delivery of radiation, but it is rarely standard in low-resource centers because it requires specific software for 3D planning, adept medical physicists, dosimetrists, and equipment, all of which are resources that are inaccessible for some centers [6,48]. Centers with low-resource settings, as shown, might not have the wide variety of imaging and treatment plans that other centers have. For this reason, adaptation to treatment plans must be made. For example, CT-based imaging and hybrid imaging are used when MRI access is little; even then, a diagnostic MRI without the applicator provides many benefits, including consistent HR-CTV contouring, paving the road for IGBT [6,9,17,49].

Strengths and limitations of this review

This narrative review allows for discussion regarding treatment plans, clinical staging, and technical considerations in brachytherapy. By using evidence from radiation oncology and gynecologic oncology, evidence is presented in a multidisciplinary perspective that is rarely highlighted in the literature regarding brachytherapy.

Because this study is not systematic, may be bias. This review focused on a qualitative framework that didn't include formal statistical analysis. For this reason, specific implementation suggestions are intended to provide a framework for the possibilities of different, referral decisions, and treatment pathways.

Conclusion

Brachytherapy is a vital part of definitive cervical cancer treatment, and personalized treatment plans are imperative for achieving the objective. While ICBT remains the standard of care for most cervical cancers, ISBT and HBT approaches remain important treatment options for locally advanced diseases. Newer techniques such as HBT and IGBT have been shown to address variances in patient anatomy and tumor geometry, resulting in better tumor dose coverage and improved outcomes. Looking ahead, recent publications highlight AI's potential in brachytherapy for cervical cancer treatment. Through automatic segmentation, applicator reconstruction, dose calculation, and plan optimization, AI can standardize quality, accelerate workflow, and make such advanced techniques more accessible [50]. As these systems grow, integration with radiomics and other imaging biomarkers could enable real-time planning and individualized dose prescription, furthering personalized care for each patient.

Author contributions

Arjun Moorthy - Conception and design, Data analysis and interpretation, Manuscript writing, Final approval of manuscript.

Ayan Issac - Collection and assembly of data, Manuscript writing, Final approval of manuscript.

Ngoc-Anh Le - Collection and assembly of data, Administrative support, Manuscript writing, Final approval of manuscript.

Kavin Mutyala - Collection and assembly of data, Manuscript writing, Final approval of manuscript.

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Shyamal Patel - Conception and design, Manuscript writing, Final approval of manuscript.

Lyndsay Willmott - Conception and design, Manuscript writing, Final approval of manuscript.

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