

Evolution of Brachytherapy Applicators for the Treatment of Cervical Cancer

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Abstract

Brachytherapy applicators have come a long way since Danlos developed early intracavitary applicators to treat cervical cancer patients. Therefore, this review will help in the neoteric designs of intracavitary applicators. A detailed literature survey of the gynecological brachytherapy applicators from the era of preloading to conceptual intensity-modulated brachytherapy applicators has been carried out. Depending on the extent of the disease and patient anatomy, the selection of brachytherapy applicators plays a pivotal role in the treatment of cervical cancer. Furthermore, the selection of the applicators is also based on the imaging modalities to be used for applicator reconstruction and treatment planning. Dose acceleration in the target and reduction in nearby organs at risk can be optimized using an applicator having the capabilities of intensity-modulated brachytherapy. Now, three-dimensional printed applicators are used for patient-specific tailor-made treatment and they are fast replacing the old conventional applicators. Newer advancements in technology have greatly influenced the neoteric designs of intracavitary brachytherapy applicators.

Keywords: Brachytherapy applicator, brachytherapy device, cervical cancer brachytherapy, gynecologic brachytherapy, three-dimensional printing

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INTRODUCTION

The use of radioactive substances in medicine was started when Pierre curie gave a small amount of radium to Dr. Henry Alexander Danlos with a suggestion that it can be used to treat various pathologies conditions. Danlos early trials motivated the development of the first applicators to fit the various purposes of surface and intracavity applications. Subsequently, in 1903, Alexander Gram Bell suggested the use of radium sealed in a glass tube that could be inserted inside the carcinoma tumor for treatment.

Intracavitary irradiation for cervical cancer in the early years was fraught with complications. However, with clinical experience and improvement in the designs of the applicator, such complications have diminished and the cure rate of cancer has improved.^[1-3] The treatment of cervical cancer has been highly effective with the combination of intracavitary and external irradiation, for the early and advanced stages.^[4] Sequelae and complications have been reduced to a minimum by the judicious use of correct applicators (intracavity or interstitial), careful placement of the applicators and proper

selection of radioactive sources. In the due course of time, brachytherapy (BT) applicators have evolved distinctly into a high-end technology modality of radiation therapy, that incorporates three-dimensional (3D) imaging and sophisticated planning methods as the standard of care.^[5,6]

PRELOADED APPLICATORS

Danlos used radium for treatment in 1901 and developed the first intracavitary applicator [Supplementary Figure 1a].^[7,8] He handed over radium applicators to Dr. Wickham with 150 mg of radium. Wickham incorporated the radium into a water-resistant varnish that could be melted, poured, or painted over a variety of flat, square, or round copper receptacles [Supplementary Figure 1b-d].^[9]

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His applicator resembled an inverted umbrella with an intrauterine stem screwed into the concave inner center of the vaginal portion. The stem and the concavity were painted with the radioactive varnish and the whole applicator was covered with a sheath of lead for filtration.^[9]

These primary practices recognized the use of ionizing radiation in medicine and clinicians established their own rules for the treatment of cervical cancer. The treatment given by different clinicians was not the same; therefore, Stockholm, Paris, and Manchester Systems were evolved. All these systems have their own applicator design, set of rules for activity distribution, and dose prescription.

STOCKHOLM SYSTEM

Stockholm system appeared in 1910 and was modified subsequently.^[10-12] It consisted of an intrauterine tube and vaginal box applicator made up of rubber and silver/gold. Intrauterine and vaginal applicators were not connected to each other [Supplementary Figure 2]. A semifixed geometry combination of both applicators was used during the intracavitary application with help of gauze packing.^[13] The vaginal applicator was held against the cervix and lateral fornix by gauze packing to reduce the rectum and bladder doses.

For the treatment of cervical cancer, both applicators were loaded with radium-226 (²²⁶Ra).^[14] The intrauterine rubber tube and vaginal boxes were preloaded with 30–90 mg and 60–80 mg radium-226 radioactive sources of solid linear tubes. Unequal loading of the source was done in the intrauterine tube and vaginal sources. Total mg-hrs usually ranged from 6500 to 7100 mg-hr, out of which 4500 mg-hrs was approximately in the vagina. The modified Stockholm method used a larger amount of radium to reduce the treatment time to 10–18 h for each treatment.^[15] This loose and flexible applicator had the advantage of easy insertion into the cervix but at the same time had the possibility of slippage and a change in geometry after insertion. These applicators were preloaded with radioactive sources; therefore, it was hazardous to handle them.

PARIS METHOD

Regaud and its associate at the Institute of Radium Paris developed the Paris Method in 1919.^[16,17] It consists of two cork colpostat, connected by a transverse metal spring and positioned in lateral fornix perpendicular to the intrauterine tube.^[18] A hollow rubber elastic tube was used in the uterine cavity. The intrauterine tube contained three sources in the ratio of 1:1:0.5 i.e. 13.33:13.33:6.66 mg of radium-226 [Supplementary Figure 3]. Two colpostat intravaginal cylindrical applicators were loaded with equal amount (13.33 mg) of two Radium-226 sources.^[19,20]

An equal amount of radium-226 source was used in the uterus and vaginal applicator. The treatment used to be completed in a single fraction to deliver a dose of 7200–8000 mg-hrs. The product of source mass and duration in units of mg-h

was fixed. Vaginal applicators were connected with a flexible spring having a rubber coating. Uterus and vaginal applicators were not fixed together. In this method, dose prescription was in terms of mg-hr, therefore, there was a lack of information about the actual dose to the tumor and the organs at risk (OAR). However, the actual dose was later found to be 6,150 roentgen at Manchester Point A.^[21]

MANCHESTER SYSTEM

Tod and Meredith developed the Manchester system in 1938 and introduced Point A for dose prescription. Initially, Point A was defined as a point 2 cm lateral to the central canal of the uterus and 2 cm up from the mucus membrane of the lateral fornix, in the axis of the uterus.^[21]

During the era of X-ray radiographs, dose calculations were done with the help of radiographs and localization of Point A was difficult because the surface of the ovoids was not visible. Therefore, they revised this system in 1953 to locate Point A from 2 cm up from the flange or lowest most source of intrauterine tandem and 2 cm lateral from the central canal.^[22]

In this system, the intrauterine applicator made up of thin rubber or plastic hollow tubes with the superior end closed and flange present at the lower end. It was available in three lengths 2 cm, 4 cm, and 6 cm, which was used depending upon the length of the uterus^[23] [Supplementary Figure 4]. Different intrauterine tube lengths were meant for one, two, or three radium tubes.

The vaginal applicators were called ovoids, made up of hard rubber or plastic with different varying diameters called small, medium, and large ovoids. The ovoids were placed at each lateral vaginal fornix at the level of the cervix and tied by thread with the help of a rubber spacer or a washer to fix them snugly. A washer was used for intermediate vaginal size and a spacer with large ovoids was used for large size vagina.

The Manchester applicators were designed in such a way that Point A received the same dose rate irrespective of the intrauterine tube and ovoid combination. Therefore, this system and applicators became more popular than previously available applicators. This system also formed the basis of the modern intracavitary brachytherapy application and dose specification methods. However, the definition of Point A has been revised with the change in the design of the applicators and techniques. Due to this, the comparison of clinical data between different brachytherapy centers became difficult.

Applicators used in Stockholm, Paris, and Manchester systems were not fixed to each other. Therefore, applicator geometry used to change due to the slipping of applicators after insertion which resulted in the change of spatial dose distribution. All these systems used preloaded Radium applicators which were hazardous to staff. The treatment time was also longer because of the low dose rate. To overcome these limitations, the development of rigid and fixed geometry preloaded and

afterloading applicators were designed.

FLETCHER FAMILY TANDEM AND COLPOSTAT/OVOID SYSTEM APPLICATOR

Fletcher applicators were inspired by the applicators used in the Manchester system but with improved design. Fletcher System was established in 1940 and the Fletcher applicator was developed in 1952.^[24,25] This applicator was further refined by Dr. Herman Suit and Dr. Luis Delclos.^[26,27] Therefore, these applicators are called Fletcher Suit Delclos (FSD) applicators [Supplementary Figure 5].

FLETCHER APPLICATOR (PRELOADED)

These preloaded applicators were made up of stainless steel with cylindrical shape ovoids. Each ovoid has its discrete tube, which facilitates the movement of the ovoid anteriorly or posteriorly as per the patient's anatomy. Ovoid tubes were held together with a scissors-type joint to vary the distance between them.

Tungsten shielding was located on the medial aspects of the anterior and posterior ovoids to minimize the dose to the bladder and rectum. However, the disadvantage of the Fletcher applicator was uncertainty in dosimetry due to the presence of shielding material in the ovoids.

AFTERLOADING APPLICATORS

Afterloading technique came in the 1960s and practiced by Ulrich Henschke^[28] and Suit *et al.*^[26]

FLETCHER-SUIT APPLICATOR (AFTERLOADING)

To minimize the radiation hazards to the personnel, the preloaded Fletcher applicator design was improved by Suit in 1960 for the Radium afterloading system and in 1970 to accommodate the Cesium-137 radioactive sources. There was difficulty in afterloading the sources in ovoids because the longitudinal axis of the radioactive source was aligned with the longitudinal axis of the ovoid. To overcome this problem, he designed the ovoids with square handle. For the smooth passage of radium sources around the bend at the point where the handle was attached to the ovoid, the radium carrier tube with a double hinge system was used [Supplementary Figure 5]. There was no cap to close over the radium tube carrier for the ovoids, as compared to the preloaded applicator. Therefore, loading and unloading of the radium carriers with this system was quicker than standard preloaded Fletcher applicators. However, the hinge mechanism in the source carrier was fragile, therefore, the radium source carrier design was modified and a radium tube was attached to the end of the wire or spring.

A cervical stopper was used in the central tandem to decide the length of tandem required to be inserted in the uterus. It was also used as an external os marker.

DELCLÓS MINI-COLPOSTAT APPLICATOR

The stainless steel Delclos Mini-Colpostat was developed for use in the narrow or tortuous vaginal cavity in 1970. There were no nylon caps that fit over the colpostat to act as spacers for the vaginal wall. In the original design (for Radium source) they do not have shielding because of a lack of space for radium tubes. However, shielding was present in the mini-colpostats constructed for small cesium sources.^[29] The dose to the vaginal wall was higher with mini-ovoid as there was no spacing effect because of the absence of nylon caps.

FLETCHER-SUIT-DELCLÓS

The Fletcher-Suit-Delclos has two designs mini and FSD. The Fletcher Suit mini applicator was similar to Delclos mini-colpostat design for the Cs-137 source except for partial tungsten shielding in the ovoids.^[30,31] If the additional 2 cm nylon cap with half-moon tungsten shielding is added to the mini colpostat/ovoid then it was known as FSD ovoid.^[32] To reduce the dose to the vaginal mucosa, additional spacer caps of 2.5 cm and 3.0 cm were available to fit over the colpostat. These spacer caps were used to push vaginal mucosa away from the radioactive sources. Fletcher ovoids were independently dilated up to the fornices. Fletcher family applicators are rigid and might cause perforation in the uterus if a large force is applied for the insertion of the intrauterine tube.

HENSCHKE APPLICATOR

Henschke afterloading intracavitary applicator was also inspired by Manchester intracavitary system and came in 1960.^[28,33] Henschke developed an afterloading flexible applicator system, particularly for cobalt 60 sources. It has a central plastic uterine tube and two spherical plastic ovoids for the lateral vaginal fornices.

Initially, it was designed without shielding material, but later on, shielding was added to protect the rectum and bladder [Supplementary Figure 6].^[34]

The ovoids were made up of nylon having 2 cm diameter and with the addition of nylon caps, the diameter could be increased to 3 cm. In the ovoids, sources were loaded through their handles (tandems) and placed parallel to the central tandem. Due to different orientations of the sources in ovoids and shielding design, the dose distribution was different than FSD applicators.^[35]

TANDEM AND RING APPLICATOR

The ring and tandem applicator was developed as an afterloading device.^[36-38] Its design was an adaptation of the Stockholm tandem-and-box technique. At that time metallic ring applicators existed in variable diameters (26, 30, 34 mm diameters). The radius of the ring was measured from center of the ring to center of the source) [Supplementary Figure 7].

This applicator has different lengths (20, 40, 60 mm) and angles (30°, 45°, 60°) of the intrauterine tube.

The ring remained perpendicular to the tandem and having predictable geometry because the tandem was fixed in the center of the ring.^[39] Acrylic caps cover over the metallic ring tube used to reduce the dose to the vaginal mucosa. The ring applicator is ideal for patients with shallow lateral fornices, partial or complete loss of the vaginal fornix. The flange is not used in the ring applicator. The tandem-ring applicator provides a pear and banana-shaped isodose distribution in coronal and sagittal view that is similar to a tandem-ovoid applicator.

The radioactive sources loaded in the ring of the tandem-ring applicator simulates the nearly same dose distribution as sources loaded in the two ovoids of the tandem-ovoid applicator. The ring substitutes two ovoids of the tandem-ovoid applicator.^[40] Insertion of ring applicator is difficult as compared to ovoids and especially in a patient with a narrow vagina.^[41] The ring has a fixed size inside the patient whereas the separation between two ovoids can be varied to modify the dose distribution.

MOLD APPLICATOR

Mold technique for intracavitary developed in 1966 at the Institut Gustave Roussy in Villejuif Cedex, France.^[39,42,43] In this technique, individualized applicators are designed to adapt to the patient's anatomy. It consists of a tandem for the uterus and mold for the vaginal part. To prepare the vaginal mold, a thin strip of gauge piece is inserted up to the vaginal fornices and then an Alginate compound is poured into the vagina. The Alginate compound becomes rigid after few minutes and an impression of a vagina is created. The vaginal mold takes the impression of the tumor, vagina, and cervix. This vaginal impression is immersed in liquid plaster. When it dries, the solid plaster is split into two parts and the vaginal impression is removed. The internal surface of the two split parts is covered with separating varnish. The acrylic applicator is made by pouring auto-polymerized synthetic resins (e. g. Palapress). When this resin dries, the two plaster pieces are removed and the mold is ready to make the intracavitary applicator.

The planned locations of the vaginal catheters are drawn on the surface of the mold, considering the target volume and patient anatomy. Two plastic vaginal catheters are fixed and immobilized on the internal surface of the molded applicator. A hole at the level of the cervical os is made through which the intrauterine catheter is passed.

Multiple holes made on the surface of the mold keep it immobilized and adhere to the mucosal membrane of the vaginal wall. The holes also help in the circulation of the fluids used for vaginal irrigation. Additional holes are drilled at the distal extremity of the mold for suturing purposes. Radioactive sources are placed through vaginal catheters and intrauterine tandem [Supplementary Figure 8a].

The plastic catheters in vaginal fornices are either parallel or circumferential. If sources are circumferential then it is

known as Creteil Method. In the Creteil method, the length of each vaginal source was 0.8 times the diameter of the cervical impression [Supplementary Figure 8b]. The radioactive sources in the vagina were positioned circumferentially at 7 mm from the left and right external lateral walls of the mold. The sources were not loaded in the anterior and posterior region to minimize the dose to the bladder and rectum. At the level of the vaginal sources, clinicians select the reference isodose to prescribe the dose at 7 mm from the surface of the mold, and 7 mm from the extremity of the intrauterine radioactive source [Supplementary Figure 8c]. Two lead beads are placed in the mold, one anterior and the other posterior to the external os. The cervical dose is calculated at the level of these lead beads.

The mold applicator delivers personalized tailored treatment, the vaginal packing is not required, and insertion of the applicator is without anesthesia. The limitation is that one applicator cannot be used for another patient.

AMERSHAM GYNECOLOGICAL APPLICATOR

Amersham International introduced the Cesium-137 manual afterloading system in 1978 and its design was inspired by the Manchester system applicator.^[44,45] It consists of central tandem, ovoids (fixed to vaginal tandems), flange, washers, and spacer. These disposable applicators are made up of semi-flexible plastic material [Supplementary Figure 9]. The biggest advantage of these applicators was that they could be adjusted as per the anatomy of the patient. These applicators were inexpensive, sterilized, and disposable. However, they have the problem of rotation inside the patient after insertion.

HIGH DOSE RATE APPLICATORS

The miniature size of the iridium-192 source facilitated the reduction of the tandem diameter to 3 mm as compared to 6 mm in the case of the LDR applicator. The smaller diameter applicator is easy to insert and causes less discomfort to the patient. Therefore, many HDR applicators with less diameter were developed such as tandem and ovoid/Ring, mold applicator, etc.

INTRACAVITARY-INTERSTITIAL BRACHYTHERAPY APPLICATORS

Conventional intracavitary applicators alone are not suitable to deliver adequate dose to the large tumors in the region of parametrium and lower vagina without crossing the tolerance doses of OARs (organs at risk). Therefore, IC-ISBT applicators were developed to give an adequate dose to the bulky infiltrative disease, asymmetric tumor growth, and vaginal spread.^[46,47]

Prefabricated perineal templates are also available through which needles are inserted inside the tumor for the treatment of advanced diseases or distorted anatomy. The template allows the insertion of a needle across the entire perineum through a

perforated template and shapes the isodose to encompass the tumor volume and spare the OAR.

Commonly used early IC-ISBT applicator for gynecological interstitial implantation are the Syed-Neblett template and the Martinez Universal Perineal Interstitial Template (MUPIT). Modern IC-ISBT applicator are Utrecht, Vienna, Split Ring, Venezia, Geneva etc.

MARTINEZ UNIVERSAL PERINEAL INTERSTITIAL TEMPLATE

MUPIT was developed for a multi-site single template for an intracavitary-interstitial applicator having an Octagon shape. Initially, it consisted of a flat template, cover plate, and obturators made up of acrylic material having multiple holes. However, currently, it is made up of polyphenyl sulfone (PPSU) (MUPIT, Elekta AB, Stockholm, Sweden) [Supplementary Figure 10a-d].^[48]

Three large holes are located along the vertical central axis of the template for the passage of Foleys catheter (upper one), vaginal obturator (middle one), and rectum obturator (lowermost). The size of the rectal and vaginal obturators is the same (13 cm in length and 2.5 cm in diameter). There are holes in the four corners of the template to suture it to the patient.

There are multiple holes (guide holes) in the template at a 1.25 cm distance from each other for the insertion of the trocar needles for transperineal insertion. The even and odd horizontal row consists of two different angles for guide holes. In odd horizontal rows, guide holes are perpendicular to the template used for straight placement of the needles, which allows a volume extending 4 cm to either side of the midplane.

Even horizontal rows, guide holes are 13° laterally outward oblique angle to the template allows wider volume coverage of parametrial or pararectal tissue with the prevention of ischium perforation during procedure. Even rows having oblique needles allow a volume extending 7 cm to either side of the midplane.

The vaginal obturator [Supplementary Figure 10c] is used to treat the vaginal surface, and it can be loaded with stainless steel needles to encompass disease from the fornix to the introitus. In case of intact uterus, both intrauterine tandem and interstitial needles along with vaginal obturator are used to deliver high dose to the cervix.

The tumor coverage is better with MUPIT and it avoids a central low dose area, in cases where an intrauterine tandem applicator cannot be inserted because of fibrosis or advanced-stage disease.

However, the delineation of OAR and CTV during the planning becomes difficult as CT images have artifacts due to metallic needles.^[49] The length of the stainless steel trocar needles is only 20 cm that limits its ability to reach beyond the cervix and needles are not MRI compatible. To overcome these limitations

of the MUPIT applicator, Benidorm Template was developed with MR compatible titanium needles.^[50]

SYED-NEBLETT GYNECOLOGICAL TEMPLATE

A. M. Nisar Syed and David Neblett introduced initially a butterfly-shaped template for interstitial gynecological brachytherapy.^[51] It consists of two thick lucite plates which are joined each other by Allen head screws. On the plate, one large and several small holes are grooved. Small holes are grooved in five concentric circles, one on the periphery of the vaginal obturator and the other four on the template.^[52]

A large hole is for the insertion of the plastic vaginal obturator having 2 cm diameter and 15 cm length and it can accommodate interstitial needles (Syed-Neblett Gyn Template, Best Medical International, Virginia, USA) [Supplementary Figure 10e]. Inside the vaginal obturator, a hole is present for the insertion of the intrauterine tandem. The intrauterine tandem is fixed to the vaginal guide by tightening a screw. In this template, conventional intravaginal ovoids are replaced with interstitial needles, which are implanted through paravaginal and parametrial tissue. This template is available with 15 or 17 gauge stainless needles. Small doughnuts shaped rubber O-rings are placed surrounding the guide needle holes to immobilize the needles. Rubber O-rings are flattened when the Allen head screws in the lucite plates are tightened.^[53]

In another technique, the steel needles are lubricated by dipping in alcohol and inserted in the guide holes of the template. After a few minutes of insertion, the alcohol evaporates and the needles get fixed at their respective position due to friction.

The use of this template is easy as compare to MUPIT but it does not have the provision of oblique needles. Therefore, the tumor coverage is limited as compare to MUPIT. Patients with locally advanced cervical cancer unsuitable for conventional ICBT can be treated with ISBT using these perineal templates.^[54,55]

COMPUTED TOMOGRAPHY/MAGNETIC RESONANCE COMPATIBLE APPLICATORS

Image-guided brachytherapy is becoming popular for the treatment of cervical cancer and treatment planning is done on the images obtained with computed tomography (CT) and/or magnetic resonance imaging (MRI). Therefore, the requirement for CT/MR compatible brachytherapy applicators has increased. However, metallic applicators and inbuilt shields inside the ovoids generate streak artifacts on CT images. Image quality is also deteriorated due to beam hardening and photon starvation. Reconstruction of applicator and contouring of structures on deteriorated images affect the quality of planning.

To address the issue of streak artifacts in CT images, some authors used applicators made up of low atomic-number materials as it minimizes photoelectric interactions and the subsequent sudden attenuation discontinuity at the tissue/

applicator interface. Therefore, FSD applicators were constructed using acrylic material with afterloaded shields.^[56] Distortion in acquired CT images happened when the metal components of ovoids interfere with 3D-imaging modalities. The shielded applicator overcome these issues by incorporated removable shielding in the ovoids.

For CT compatible applicator, Week's *et al.* made tandem and ovoids of black anodized aluminum and the handles were of stainless steel.^[57] The external dimensions of the ovoids were the same as those of mini Delclos ovoids. To avoid the artifacts from tungsten shielding in the ovoids, the CT scan of the patients were taken without shielding material.

The use of low Z (atomic number) material to design a uterine tandem becomes difficult because these materials are not as strong as high atomic numbers metals. Therefore, material like PPSU or Epoxy Polyvinyl ester polyester glass fiber is used for CT/MRI compatible applicator that makes the intrauterine tube of less diameter (4 mm) in proximal portion for the HDR applicator.

Modified values of CT window and level were used in standard shielded FSD applicators, to reduce the appearance of the artifact on the CT image for delineation of the bladder and rectum boundaries with respect to implanted applicator.^[58] Metal artifact reduction (MAR) algorithm based on Projection interpolation methods and hybrid approaches were used to minimize the metal artifacts produced by the applicator.^[59,60]

The image based CT planning complemented with MRI has benefited over a CT-only methodology.^[61] As the use of MRI-assisted brachytherapy has improved local control and overall survival.^[62] However, CT and MRI compatible applicators with the absence of ferromagnetic materials are required for imaging. Therefore, applicators made up of graphite, plastics, titanium, etc., are used.

Applicator reconstruction of titanium applicators is more challenging than that of plastic applicators due to artifacts. The size and appearance of the artifacts in MR images also depend upon the magnetic field strength, the orientation of the metal applicator relative to the main magnetic field, magnetic susceptibility, and the pulse sequence parameters.^[63] The shields in the ovoids create magnetic susceptibility artifacts due to perturbations in the homogeneity of the applied magnetic field, resulting in image distortion. The susceptibility artifacts caused by the titanium metallic tandem can be substantial with spin-echo sequences with short echo times.^[64] Bloom or ballooning artifacts at the tip of the tandem applicator may introduce geometric uncertainties in the applicator reconstruction. In addition, the diameter of an applicator may appear 2 times larger than its original diameter.

The Orthopedic metal artifacts reduction (O-MAR) sequence with view angle tilt (VAT) and slice encoding for metal artifacts reduction sequence (SEMAC) is used to improve the delineation of the titanium brachytherapy applicator in MR images. O-MAR also minimizes susceptibility artifacts

in T2W images produced by metal fiducial markers and blooming artifacts in proton density weighted (PDW) images.^[5,65] The artifacts from titanium applicators improve at the tip of the tandem and its source–pathway reconstruction when T1-weighted MR images are used with minimal slice thickness.^[64]

Modern CT/MR Applicators use strong composite fiber tubing and plastic to avoid image distortion in CT and MR images. The applicator-modeling module available in the treatment planning system is used to reconstruct the applicator as per its actual dimensions. Catheters containing copper sulphate (CuSO₄) are clearly visible in plastic applicators on T1W and T2W MR Images. Phantom study on MR and CT images of the titanium applicator/needles help to evaluate the applicator geometry relative to the artifact pattern generated on MR images.^[66] Modern designs of Henschke [Figure 1a], Ring [Figure 1b], and Fletcher applicators are now compatible with miniature HDR sources as compared to LDR sources. The modern Fletcher [Figure 1c], Fletcher Shielded (Elekta AB, Stockholm, Sweden) [Figure 1d], and Ring applicators (Elekta AB, Stockholm, Sweden) [Figure 1e], are made CT/MRI compatible by changing using the appropriate material. Other Advance gynecological applicators are Vienna Applicator (Elekta AB, Stockholm, Sweden), Vienna II Applicator,^[67] Utrecht Applicator (Elekta AB, Stockholm, Sweden), Split Ring Applicator (Eckert & Ziegler BEBIG, Berlin, Germany), MAC (Mick-Alektiar-Cohen) Applicator (Eckert & Ziegler BEBIG, Berlin, Germany), Venezia Applicator (Elekta AB, Stockholm, Sweden), Geneva Applicator (Elekta AB, Stockholm, Sweden), Ring Tulip Applicator (Eckert & Ziegler BEBIG, Berlin, Germany), and 3D printed applicators. Brief details of various Gynecological Applicators shown in Supplementary Table 1.

VIENNA APPLICATOR

The Vienna applicator is a modified form of ring applicator having multiple holes in the ring tube to implant needles parallel to the intrauterine tandem and the circular ring is fixed to the cervix through the tandem. The holes in the ring of the Vienna applicator have a 2 mm diameter, which is at a distance of 2 mm from the surface of the outer ring. The number of holes for the needles increases with an increase in the diameter of the ring [Figure 1f].

There are nine holes in 30 mm and 34 mm diameter ring whereas six holes are there in 26 mm diameter ring. The Outer diameters of the rings are 42.5 mm, 46.5 mm, and 38.5 mm respectively. Titanium needles of 20–24 cm length are used for the interstitial implant with these templates. The tip of the needle is placed 5 mm or more above the tumor because the needle tip is blind up to 5 mm and the radioactive source cannot be placed there.^[68]

With the help of interstitial needles in the Vienna applicator, asymmetric changes in the isodose distribution can be made for better dose conformity depending upon the location of the

disease. Patients treated with this applicator show better dose distribution in target while limiting the dose to OARs (bladder and rectum).^[69] However, if the tumor is extended to lateral parametrium then it is difficult to cover it with this applicator because interstitial needles are parallel to intra-uterine tandem. This problem has been addressed in the Vienna-II applicator.

The modified form of the Vienna-I applicator is called the Vienna-II applicator and it has an additional cap, which is fixed below the vaginal ring [Figure 1g]. This cap allows the insertion of interstitial needles into the distal parametrium/lateral pelvic wall in an oblique direction of 20° angles relative to the tandem for appropriate dose coverage.^[67]

As compared to MUPIT trocar needles, the round point-shaped needles are used in the Vienna applicator to minimize tissue damage and discomfort to the patient.

UTRECHT APPLICATOR

The Utrecht applicator is a tandem-ovoid-based intracavitary as well as an interstitial CT/MR compatible brachytherapy applicator.^[70] It consists of an intra-uterine tube, a cervical stopper, and two ovoids. The applicator is made up of polyphenylsulfone. The intrauterine and ovoid tubes contain glass fiber. Each ovoid has five holes at 15° angles so that the plastic interstitial needle can be placed nearly parallel to the tandem. Ovoids act as a template for the placement of the plastic needle. Each ovoid has three holes in the lateral direction at 7 mm apart from each other, one each in ventral and dorsal direction [Figure 1h]. On average 6 needles per BT fraction are sufficient to achieve the planning objectives.^[71]

SPLIT RING INTRACAVITARY APPLICATOR

The Split Ring Applicator can be used as a ring applicator or it can be split into different symmetric or asymmetric diameter distances as per patient anatomical variations of the vaginal canal and shape. Insertion of this applicator is easier than ring applicator. For a narrow vagina, each split ring can be inserted independently and splayed laterally producing an inter-ring diameter between 3.5 and 7.0 cm.

The applicator is made up of medical-grade titanium alloy with 6% aluminum and 4% vanadium. The patients with titanium applicator can safely undergo both CT and MRI scanning for treatment planning.

It has disposable/reusable build-up silicon rubber caps to fit a wide variety of anatomies. The intrauterine tandem has different sizes (2–8 cm) to accommodate the different uterine lengths. An adjustable rectal retractor having a lever-like mechanism to depress the rectal wall removes the need for packing.

Ellis interstitial caps placed over the split ring applicator help in improving the tumor coverage and prevent normal structure rupturing from the interstitial needle.^[72] The custom interstitial caps are independently attached to the upper surface of each

split ring. Each cap contains 10 equally spaced holes in the inner and outer ring through which the interstitial needles are inserted to cover the large tumors [Figure 1i]. It has the advantages of a ring applicator as well as ovoids. The ring is split into two, therefore insertion is easy and space between two halves of the ring can be increased to modify the dose distribution.

MICK-ALEKTIAR-COHEN APPLICATOR

MAC applicator design consists of a vaginal cylinder, intrauterine tandem, and template for the insertion of the interstitial needle. It has holes in the concentric circles for the placement of the needles in a straight and oblique direction [Figure 1j] to treat disease in the region of the cervix, vagina, and parametrium.

VENEZIA APPLICATOR

It is a hybrid applicator with capabilities of intracavitary and interstitial brachytherapy and was introduced in 2017.^[73,74] Patients with large or asymmetric tumor can be treated effectively with this hybrid applicator.^[75]

It consists of an intrauterine tube, interstitial lunar-shaped ovoids when connected together form a ring. The posterior portion of each lunar ovoid consists of alphabetic letter numbering from A to H for placing straight and oblique interstitial needles alternatively [Figure 1k].

Below the Lunar ovoids, a cap (resembling cylinder) can be attached to treat the vaginal wall disease. Perineal template attachable with Venezia applicator helps to spread the needle across the vaginal extension. The perineal template helps in implanting the needles in the desired geometry.^[76] Venezia applicator assembly is fixed quickly without screws. A fixation clamp is used to fix the uterine and lunar ovoid tandems. Venezia applicator is compatible with ultrasound, X-ray, CT, and MR imaging modalities. The insertion of the Venezia applicator is easy and it significantly improves dose coverage to the tumor while at the same time sufficiently spares organs at risk.

GENEVA APPLICATOR

Its design is inspired by Henschke, Rotterdam, Standard Fletcher and Utrecht applicators. The cervical stopper is integrated with the central tandem, which avoids the chances of its slippage from the intrauterine tandem. To treat the asymmetric disease around the ovoid region, an interstitial template is provided beside the ovoid to accommodate the interstitial needles [Figure 1l]. This applicator has the facility to insert a flexible interstitial tube through the cervical stopper in place of the uterine tandem. It has a rotating and click mechanism to fix the applicator assembly, which is quicker than the screw mechanism. It provides distortion-free images with different imaging modalities, as it has no metallic parts and screws.

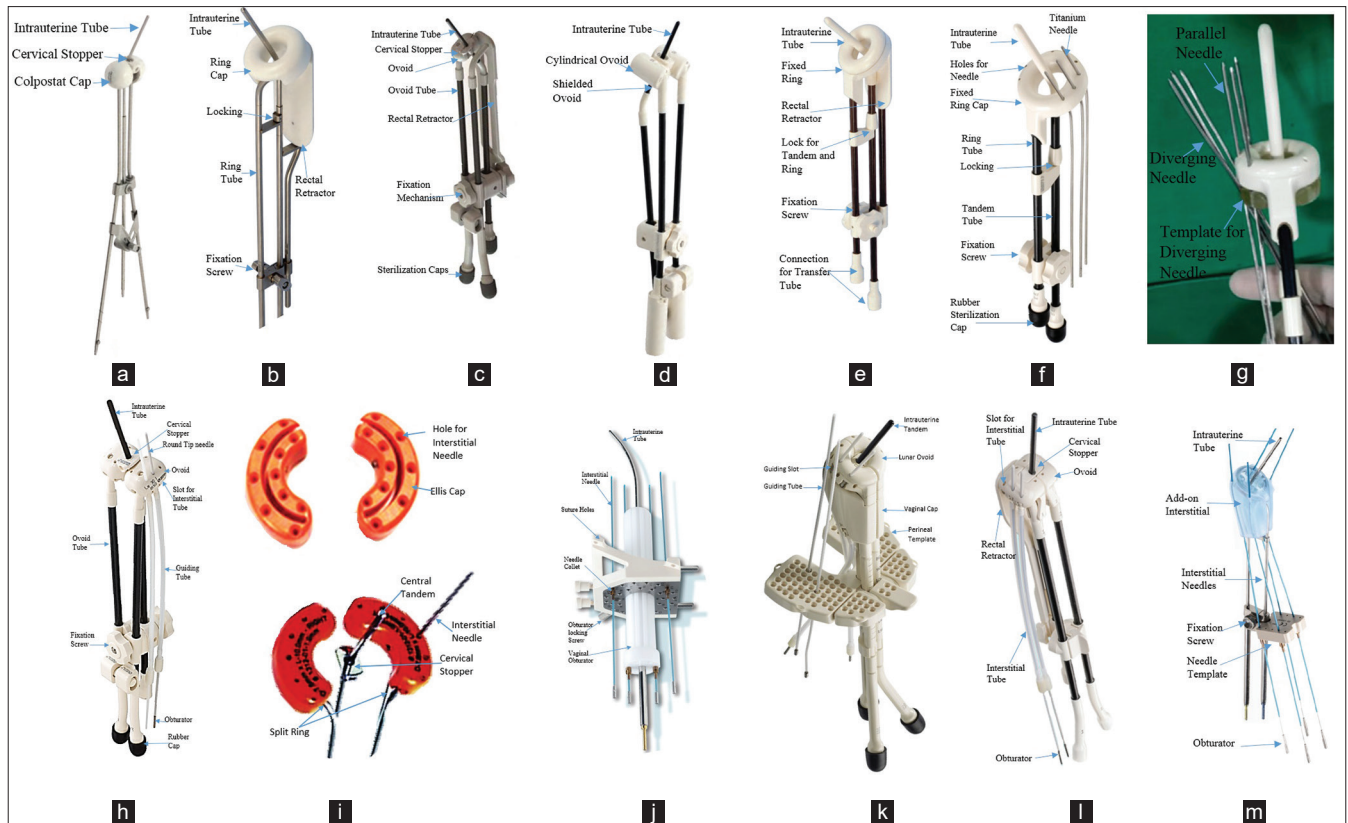


Figure 1: Modern computed tomography or magnetic resonance imaging compatible applicator. (a) Henschke computed tomography compatible applicator*. (b) Ring computed tomography compatible applicator*. (c) Fletcher computed tomography/magnetic resonance imaging compatible applicator*. (d) Fletcher shielded computed tomography/magnetic resonance imaging compatible applicator*. (e) Ring computed tomography/magnetic resonance imaging compatible applicator*. (f) Vienna applicator*. (g) Vienna II applicator.^[67] (h) Utrecht applicator*. (i) Split ring applicator #.^[72] (j) MAC applicator #. (k) Venezia applicator*. (l) Geneva applicator*. (m) Ring tulip applicator #. *: Elekta AB, Stockholm, Sweden, #: Eckert & Ziegler BEBIG, Berlin, Germany. Permission was obtained from Elekta, Eckert & Ziegler BEBIG to reproduce the figures for publication.

TULIP APPLICATOR

Any existing conventional applicator can be converted into a Tulip applicator with an add-on 3D printed kit to facilitate intracavitary as well as interstitial application [Figure 1m]. A Needle Guide system is attached distally to the conventional ring or ovoid tubes. The interstitial needle template attached to the proximal portion of the ring or ovoid work together with the distal needle guide to ensure that the implanted needles cover the target areas in the cervix or parametrium and remain at their place during treatment. It has the advantage of putting the interstitial needles parallel to the intrauterine tube as well as oblique at desired angles.

Intensity-modulated brachytherapy

Intensity-modulated intracavitary brachytherapy is achieved with the help of a shielded applicator or radiation source and it could be static or dynamic.

Static intensity-modulated brachytherapy

In S-IMBT, the intensity at a point is modulated through inbuilt static shielding design or by optimizing the dwell time and position. It can be achieved by direction-modulated brachytherapy (DMBT) applicator (Fletcher-shielded applicator, MUPIT, Venezia, Vienna, etc.). In S-IMBT,

shielding material is not moved relative to the source or surrounding tissue.

Direction-modulated brachytherapy applicator

Tungsten alloy shielded grooved rod inserted in tandem is used with ¹⁹²Ir source in direction-modulated brachytherapy applicator.^[77] The uterine tandem of DMBT is a 5.4-mm diameter tungsten alloy rod having 6 peripheral grooves (separated by 60° equidistant angles) wrapped inside a 0.3-mm thick bio-safe thermoplastic sheath [Figure 2]. Along the length of the central tandem, the source travels through these six symmetric grooves. Thin plastic tubes fitted into each groove are connected to each transfer tube for source movement as per programming of TPS. The tip of the tandem is sealed with polyether ether ketone material.^[78,79] The dynamic single-channel shields with narrow beam widths in the polar and azimuthal direction give rise to anisotropic distributions. DMBT gives directional dose profiles in the transverse and longitudinal tandem axis as compared to conventional tandem-ring applicators that produce isotropic dose distribution. Artifacts formed in CT images are reduced digitally with MAR Algorithm.^[80] Monte Carlo-based algorithm or TG-186 algorithm is required for planning to take care of heterogeneity produced by the tungsten shielding.^[81]

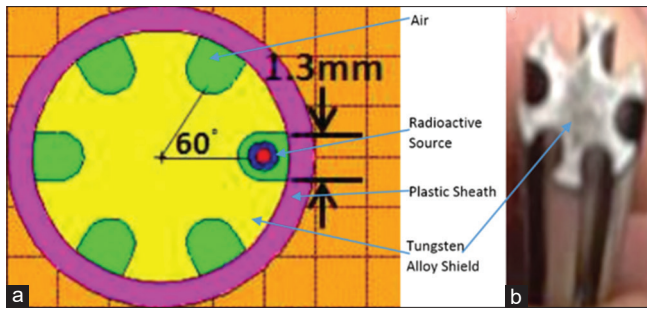


Figure 2: Direction-modulated brachytherapy. (a) Axial view of direction-modulated brachytherapy applicator (b) Actual image of direction-modulated brachytherapy applicator without plastic sheath^[78]

Dynamic intensity-modulated brachytherapy

In D-IMBT, shielding material changes its direction relative to the radiation source or surrounding tissue and it can be achieved by the following methods.

Rotation shield brachytherapy

The Rotation shield brachytherapy consists of electronic brachytherapy (eBT) source, which can be shielded inside the applicator. A partially shielded Xofigo Axxent eBT source is a miniature X-ray source that is sheathed in a 5.4 mm diameter water-cooled catheter. The tube can be operated between 20 and 50 kVp, at a standard operating voltage of 50 kV and tube current of 300 μ A. The eBT sources were used to check the feasibility of dose distribution in S-RSBT (Single-shield rotating shield brachytherapy), D-RSBT (Dynamic rotating shield brachytherapy), H-RSBT (Multi Helixrotating shield brachytherapy), and P-RSBT (Paddle rotating shield brachytherapy) applicator.

- In S-RSBT, inside the applicator, at each dwell position, the partial tungsten shield of 0.5 mm thickness is rotated to numerous angular locations around the eBT source.^[82] The treatment time is more as compared to the conventional ICBT/IS-ICBT technique and it depends upon the selection of azimuthal shield emission (ASE) angle [Figure 3a]
- D-RSBT uses two independent layers of rotating tungsten alloy shields (each 0.5 mm thick) and each shield has an opening of 180° ASE angle.^[83] During the treatment, both tungsten shields can be rotated to achieve an azimuthal emission angle of less than 180° to modulate the radiation beam. Due to the variable ASE facility in D-RSBT, more conformal dose distribution can be achieved as compared to single shield S-RSBT that uses the same ASE during the treatment [Figure 3b]
- P-RSBT uses a set of independently operated Tungsten alloy shield paddles. Intensity modulation is achieved by the insertion/retraction of these paddles and rotation/translation of the whole applicator [Figure 3c]. The set of shield paddles can move in (close) and out (open) independently to block and expose the radiation source^[84]
- H-RSBT is achieved using the linear translational motion of the source and shield combination inside a

curved applicator. Dose conformity with H-RSBT and S-RSBT are similar, but the treatment time is less with H-RSBT.^[85] The inner applicator wall contains six equally spaced helical keyways that firmly delineate the emission direction of the partial radiation shield as a function of depth in the applicator [Figure 3d].

The above techniques of RSBT are conceptually proposed for eBT source with shielded applicators and very few patients have been treated with unshielded applicators.^[86] However, the flute style [Figure 4] shielded applicator may be used to achieve intensity-modulated brachytherapy with radioactive sources.^[87-89]

D-IMBT has been demonstrated with a rotating MRI-compatible flute style shielded applicator for different radioactive sources such as ¹⁹²Ir, Selenium-75 (⁷⁵Se), and Yttrium-169 (¹⁶⁹Yb). ⁷⁵Se and ¹⁶⁹Yb sources increase the modulation potential of IMBT because their average photon energies are less than Ir-192.

THREE-DIMENSIONAL PRINTED APPLICATOR

3D printers are used to design customized brachytherapy applicators or some parts of applicators to be assembled with commercially available applicators.^[90,91] 3D printed brachytherapy applicators are designed [Figure 5a-d] from the dimensions estimated from physical examination and imaging of the patient.^[92,93] A material used for 3D printed applicator should be biocompatible, sterilizable, CT/MR-compatible, and have dose-attenuation properties similar to water.^[94] Sekii *et al.*^[95] designed interstitial templates with a 3D printer using medical images of vaginal tumors. They used Polycarbonate/acrylonitrile-butadiene-styrene (PC-ABS) polymer alloy material for the template.

Radiation attenuation properties of 3D printed brachytherapy applicators with different infill percentages of thermoplastic materials should be studied to see its impact on dose distribution.^[96] Biocompatibility of 3D printed devices can be assured by using United States Pharmacopeia (USP) Class VI or ISO standard 10993 certified materials.^[97]

3D printed applicators are beneficial for cervical patients, whose anatomy falls outside the range of currently available commercial applicators. The limitation of customized 3D printed applicators is that they can't be used for another patient.

Limitations of the review

In the literature, there are not enough studies available related to IMBT and 3D printed applicator. Therefore, their comparison with the conventional brachytherapy applicator could not be carried out in this review. With the advent of technology, heterogeneity exists in the design of the gynecological applicators, loading of the radioactive sources, radionuclide, shielding design, and imaging. Therefore, this review lacks in comparative dosimetric study based on depth dose, isodose curve, the effect of heterogeneity, and different radionuclide sources.

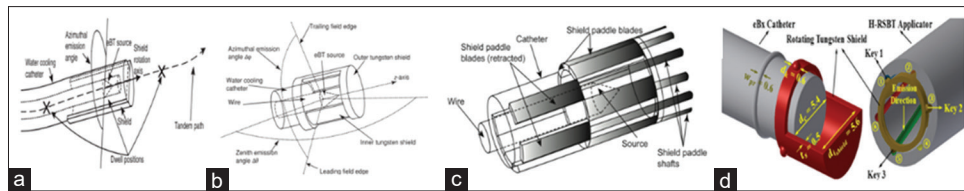


Figure 3: Dynamic IMBT (D-IMBT) applicators design based on electronic sources. (a) S-RSBT applicator design.^[82] (b) D-RSBT.^[83] (c) P-RSBT.^[84] (d) H-RSBT.^[85] IMBT: Intensity-modulated brachytherapy, RSBT: Rotational shield brachytherapy, S-RSBT: Single-shielded RSBT, D-RSBT: Dynamic RSBT, P-RSBT: Paddle RSBT, H-RSBT: Multihelix RSBT

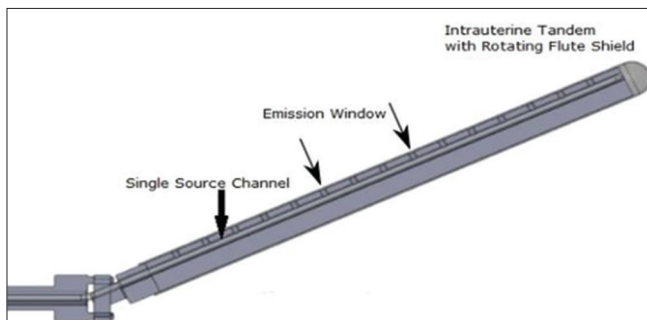


Figure 4: D-IMBT a rotating MRI-compatible flute style shielded applicator with radioactive source.^[88] D-IMBT: Dynamic intensity-modulated brachytherapy

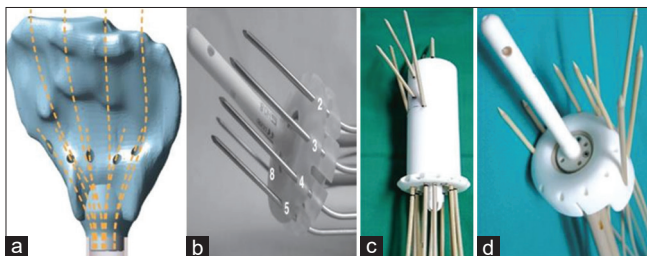


Figure 5: Designs of three-dimensional printed applicator. (a) Patent specific vaginal applicator.^[93] (b) Tandem with three-dimensional printed needle cap.^[91] (c) Multichannel vaginal cylinder with interstitial needle.^[92] (d) Tandem and ring with parallel and oblique needles

CONCLUSIONS

A detailed review of the gynecological brachytherapy applicators from the era of preloading to afterloading applicators and conceptual intensity-modulated brachytherapy applicators have been presented. The role of imaging in brachytherapy has increased; therefore, neoteric applicators try to fulfill the challenge of compatibility with all available imaging modalities. Interstitial brachytherapy helps in covering the advanced stage tumor; hence, gynecological applicators having capabilities of intracavitary as well as interstitial brachytherapy are much in demand.

Recently, intensity-modulated brachytherapy (IMBT) with shielded applicators or sources have been investigated. Theoretically, it has been demonstrated that IMBT decreases the dose to OARs and increases target coverage as compare to conventional brachytherapy. IMBT may help in the dose escalation in cervical cancer; however, this technique is in

infancy, and the rigorous testing of applicators used with clinical results is required.

The future of gynecological applicator belongs to an in-house 3D printed applicator as per the patient anatomy, extension, and location of the disease. Applicators with capabilities of intracavitary and interstitial brachytherapy with a robust mechanism of rectum and bladder retractions are the need of the hour.

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Conflicts of interest

There are no conflicts of interest.

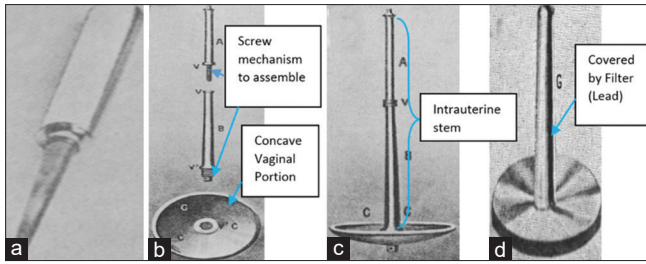
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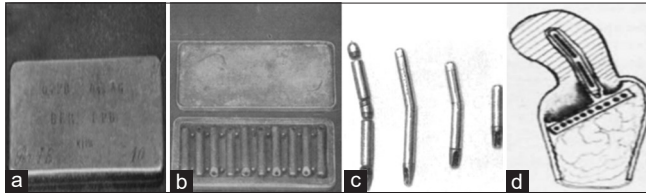
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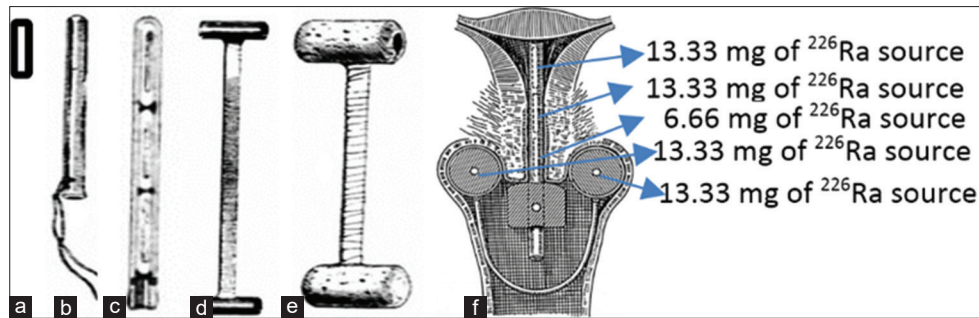
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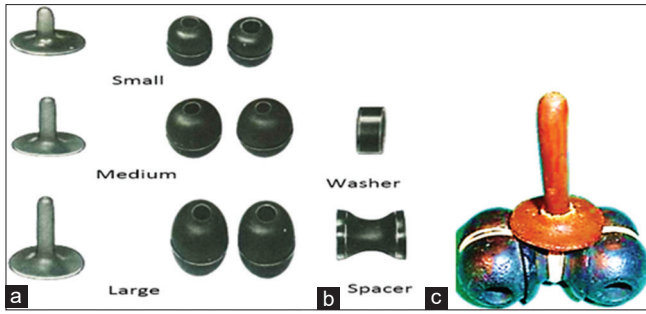
Supplementary Figure 1: Early radium radioactive source based gynecological applicator design. (a) Danlos initial intracavitary brachytherapy applicator^[8]. (b-d) Wickham applicator design^[9]



Supplementary Figure 2: Stockholm intracavitary brachytherapy applicator. (a and b) Flat Box with preloaded radium sources for vagina placement.^[13] (c) Intrauterine tube capsules of radium with variable length.^[10] (d) Sagittal view of applicator preloaded with radium sources in the intrauterine and vaginal box^[10]

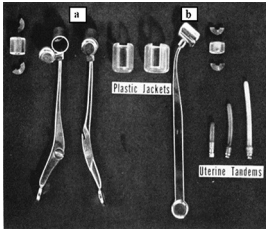
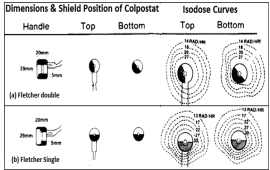
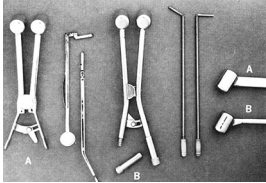
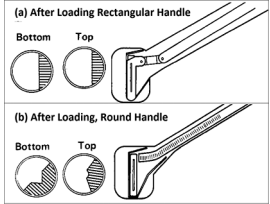
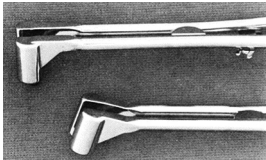
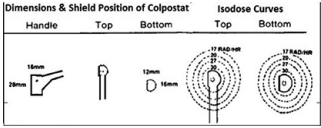


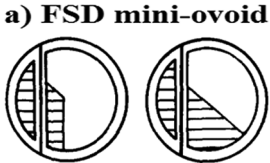


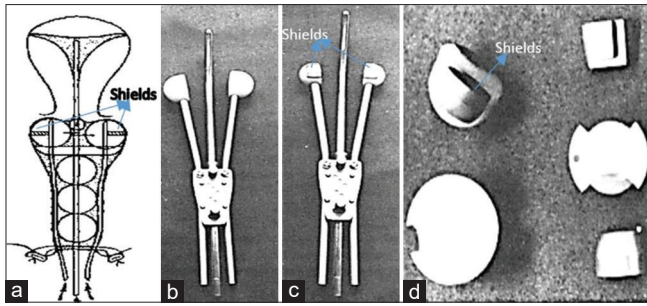
Supplementary Figure 3: Paris system intracavitary applicator. (a) Radium-226 source tubes. (b) Blind ended rubber tandem having three radium sources (1:1:0.5) i.e. 13.33 mg, 13.33 mg, 6.66 mg of radium-226 sources. (c) Metal sheath of vaginal colpostat. (d) Radium tube inside rubber tandem. (e) Two Colpostat joined contain one 13.33 mg radium-226 source in each.^[18] (f) Coronal view of whole applicator assembly inside the patient^[20]



Supplementary Figure 4: Represents the Manchester applicator. (a) Small, medium, large sizes of tandems and ovoids.^[23] (b) Washer and spacer. (c) Manchester whole applicator assembly

Supplementary Figure 5: List of Fletcher family applicators design development^[24-27,29-32]

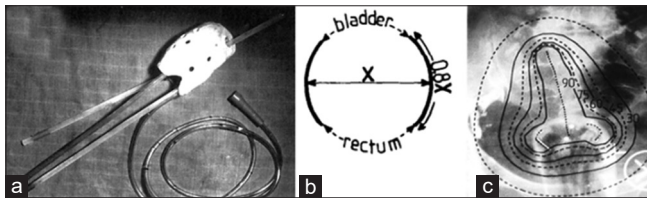
Applicator Material	Ovoids/colpostat	Schematic diagram of Ovoids
Preloaded 1950		
Fletcher Double (a) Fletcher Single (b)	Stainless Steel Stainless Steel	 
Afterloading 1960		
Fletcher-Suit (a) Fletcher-Green (b)	Stainless Steel-Rectangle Handle Stainless Steel-Round Handle	 
Afterloading Mini 1970		
Delclos-Mini	Stainless Steel and No Shields	 
Fletcher-Suit-Delclos	Stainless Steel	
FSD mini ovoid (a) FSD Ovoid (b)		  <p style="text-align: center;">a) FSD mini-ovoid b) FSD Ovoid</p>



Supplementary Figure 6: Henschke afterloading applicator. (a) Initial Design of Henschke afterloading applicator with the shield.^[28] (b and c) Modified design of Henschke applicator without the shield in ovoids and with shielding material in ovoids.^[34] (d) Ovoid caps with a slot for shielding materials



Supplementary Figure 7: Ring applicator. (a and b) Schematic diagram of early ring applicator for cervitron II and remote afterloading machine.^[36,38] (c) Applicator with rectal retractor for nucletron machine^[39]

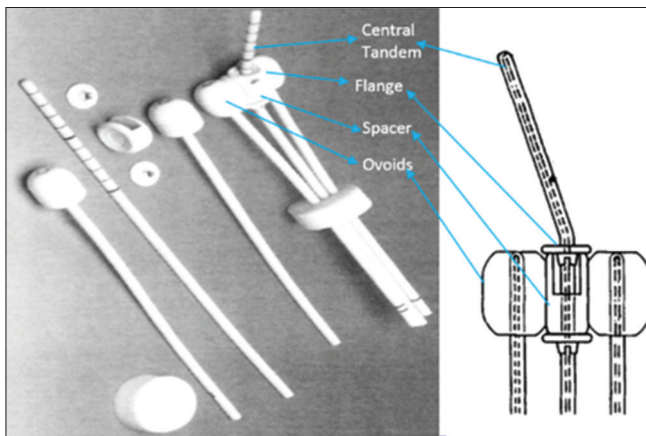


Supplementary Figure 8: Institut gustave roussy applicator. (a) Creteil method (or Chassagne and Pierquin) applicator. (b and c) Schematic diagram of source distribution in vaginal portion catheter and radiograph^[42]

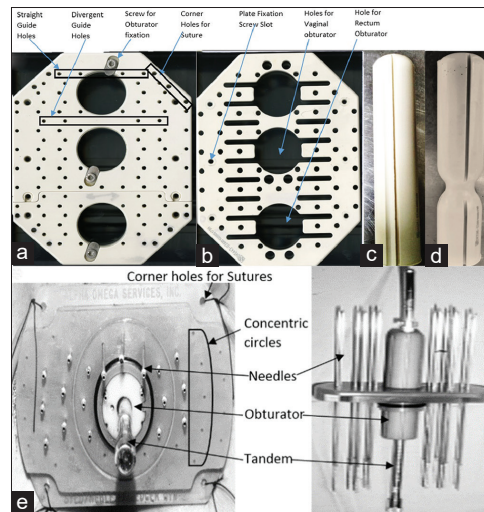
Supplementary Table 1: Brief details of various gynecological applicators

Era	Applicator name	Loading type		Application type	Clinical usage	Design
		Manual	Remote			
1900-1952	Wickham applicator	Yes	No	IC	Cervix, endometrium	T-R
	Stockholm applicator	Yes	No	IC	Cervix, endometrium	T-B
	Paris applicator	Yes	No	IC	Cervix, endometrium	T-O
	Manchester applicator	Yes	Yes*	IC	Cervix, endometrium	T-O
1953-2004	Fletcher	Yes	Yes*	IC	Cervix, endometrium	T-O with shield
	Fletcher-Suit	Yes	Yes*	IC	Cervix, endometrium	T-O with shield
	Fletcher Suit delclos	Yes	Yes*	IC	Cervix, endometrium	T-O with shield
	Henschke applicator	No	Yes	IC	Cervix, endometrium	T-O
	Tandem-ring applicator	No	Yes	IC	Cervix, endometrium	T-R
	Mold applicator	No	Yes	IC	Cervix, endometrium, vagina	T-M
	Amersham applicator	No	Yes	IC	Cervix, endometrium	T-O
	MUPIT	No	Yes	IC + IS	Cervix, endometrium, vagina, distal parametrium	T-C + TE with needle
	Syed-Neblett applicator	No	Yes	IC + IS	Cervix, endometrium, vagina, distal parametrium	T-C + TE with needle
	Fletcher-shielded applicator	No	Yes	IC	Cervix, endometrium	T-O + S
	2005 onwards (hybrid applicators)	Vienna applicator	No	Yes	IC + IS	Cervix, endometrium
Vienna II applicator		No	Yes	IC + IS	Cervix, endometrium, distal parametrium	T-R + oblique needles
Utrecht applicator		No	Yes	IC + IS	Cervix, endometrium	T-O + needle
Split ring applicator		No	Yes	IC + IS	Cervix, endometrium	T-R + needle
MAC applicator		No	Yes	IC + IS	Cervix, endometrium, vagina, distal parametrium	T-C + TE with needle
Venezia applicator		No	Yes	IC + IS	Cervix, endometrium, vagina, distal parametrium	T-R + TE with needle
Geneva applicator		No	Yes	IC + IS	Cervix, endometrium, distal parametrium	T-O + TE with needle
Tulip applicator	No	Yes	IC + IS	Cervix, endometrium, distal parametrium	T + 3D print TE with needle	

*Indicate modern design of applicator. IC: Intracavitary, IS: Interstitial, T-O: Tandem and ovoid, T-B: Tandem and box, T-R: Tandem and ring, T-M: Tandem and mold, T-C: Tandem and cylinder, TE: Template for needle insertion, T-O+S: Tandem and shielded ovoid, MUPIT: Martinez Universal Perineal Interstitial Template



Supplementary Figure 9: Amersham gynecology applicator parts and Schematic diagram of the whole assembly of it^[44,45]



Supplementary Figure 10: MUPIT and Syed-Neblett interstitial applicator. (a) MUPIT Needle template toward patient (b) Cover plate of MUPIT template* (c) Vaginal obturator* (d) Rectum obturator* (e) Syed-Neblett template applicator different parts #. MUPIT: Martinez Universal Perineal Template, *: MUPIT, Elekta AB, Stockholm, Sweden, #: Syed-Neblett Gyn Template, Best Medical International, Virginia, USA. Permission was obtained from Elekta to reproduce the figure for publication