Healthcare Professional Guide

# Brachytherapy:

*The* precise answer for tackling gynecological cancers

Because life is for living

## Radiotherapy: a cornerstone of gynecological cancer care

Gynecological cancers are amongst the most common types of cancer in women. Worldwide the yearly incidence of cervical cancer is around 530,000, and of endometrial cancer is around 287,000.[1]

Unfortunately **the mortality rates for gynecological cancers remain high** – especially for cervical cancer – predominantly due to late detection. The advent of screening programs is facilitating earlier treatment and subsequently decreasing mortality. However, advanced disease and treatment-related morbidity remain significant challenges. Innovation in gynecological cancer treatment is key to addressing the current and future needs of patient care. **Effective treatment options mean many women can achieve good cancer control and quality of life**.[2,3]

Innovation in radiotherapy continues to enhance treatment options, especially in the absence of any significant pharmaceutical advances. Scientific and technical advances in imaging modalities, computerized planning, dose delivery and innovative applicators have resulted in considerable improvements in patient outcomes, and have provided additional options in the treatment of advanced and more complex disease. **Radiotherapy** is becoming more personalized and, alongside surgery and chemotherapy, **is a cornerstone of gynecological cancer treatment.**



## Brachytherapy: treating gynecological cancers from the 'inside, out'

Radiotherapy can be divided into **external beam radiotherapy** (EBRT) and **internal radiotherapy**, frequently referred to as **brachytherapy**.

Unlike EBRT, brachytherapy involves placing a radiation source internally near to, or into, the target tissue. The precise, conformal approach of brachytherapy allows **radiation to be delivered directly to the target area, while sparing surrounding healthy tissues** and structures.[4,5]

Depending on cancer stage and characteristics, radiotherapy treatment of gynecological cancers can be delivered via brachytherapy or EBRT, or frequently a combination of both. These treatments are often combined with surgery and/or chemotherapy to obtain the best possible chance of cancer control.[2,3]

This guide provides an overview of the significant benefits of brachytherapy that make it an important part of treatment for many women with gynecological cancers.

**Benefits of brachytherapy in gynecological cancers; delivering radiation from the 'inside, out':**

- **Standard of care:** Considered a standard of care in gynecological cancers such as cervical cancer.[6]
- **Precision:** Tailored radiation dose delivered precisely to target the tumor.[7,8]
- **Demonstrated efficacy:**
  - Cancer control and survival rates equivalent to EBRT and surgery in certain tumor stages.[9]
  - Improved overall survival in cervical cancer when brachytherapy is used (in combination with EBRT)[6]
- **Minimized side effects:** Nearby healthy tissue is spared from unnecessary radiation, minimizing bowel and bladder side effects, resulting in favorable functional outcomes.[10,11]
- **Quality of life benefits:** Short treatment times and improved quality of life.[11]
- **Advancing techniques:** Brachytherapy is continually improving through advances in imaging techniques, computer-based planning technology and applicator design, leading to greater precision, efficacy and associated reduced morbidity.[12]
- **Cost-effective:** Favorable investment, maintenance and cost-effectiveness profile.[13]

# Treating gynecological cancers

Gynecological cancer 'staging' is determined by the clinical extent of the disease. Staging is used to guide treatment decisions and prognosis.

### *Cervical cancer: treatment combinations by stage*[14]

| | | |
|---|---|---|
| Early | IA1 – IB1 | Womb-sparing surgery OR hysterectomy OR radiotherapy |
| Locally advanced | IB2 – IIIB | Radio-chemotherapy +/- hysterectomy |
| Advanced | IVA – IVB | Radio-chemotherapy |

### *Endometrial cancer: treatment combinations by stage*[15]

| | | |
|---|---|---|
| Early | IA – IB | Hysterectomy +/- radiotherapy |
| Locally advanced | IIA – IIIC | Hysterectomy + radio-chemotherapy + hormonal therapy |
| Advanced | IVA – IVB | Radio-chemotherapy + hormonal therapy |

# Role of brachytherapy in gynecological cancer treatment

***Cervical cancer:*** Brachytherapy **is a standard treatment in cervical cancer.** Brachytherapy monotherapy is an **equally effective alternative to surgery in earlier stages.** In more advanced stages, **brachytherapy is used in combination with EBRT and often chemotherapy** with use of cisplatin (collectively referred to as radio-chemotherapy). EBRT treatment lasts 7–8 weeks followed by 2–5 sessions of brachytherapy.[14]

**Brachytherapy delivers the increased doses of radiation needed to help prevent recurrence, without the increased toxicity, side effects and impaired quality of life associated with using higher doses of EBRT alone.**

**The use of brachytherapy improves overall survival in patients with cervical cancer**[6]

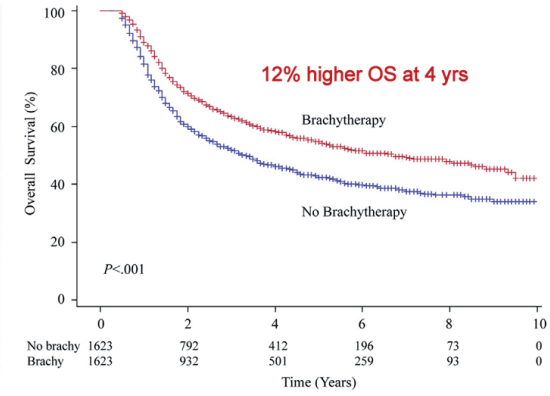


**Figure 1**

The graph in figure 1 shows the results from a recently published SEER database study which shows that the use of brachytherapy in patients with locally advanced cervical cancer (stage 1B2-IVA is associated with a 12% higher overall survival (OS) at 4 years.

***Endometrial cancer:*** Brachytherapy is typically used **in combination with surgery** in early and locally advanced stages **and as an alternative, or adjunct, to EBRT,** in intermediate to advanced stages.[16]

# Brachytherapy delivery

Brachytherapy delivers a tailored radiation dose direct to the target area with high precision while minimizing exposure to surrounding healthy tissues and organs.[9,18]

**Imaging techniques** define the target area to be treated, identifying the relationship of the target tissue to other nearby structures and organs.

Imaging techniques include X-ray, computed tomography (CT) and magnetic resonance imaging (MRI).[6]

**Specialized planning software** creates a **computerized treatment plan** to define the specifics of dose delivery.

A specialized computer controlled device, called an **afterloader**, delivers the radiation to the target tissue via specialized **applicators**.[6]

Applicators can be placed into a body cavity (intracavitary) such as the vagina, cervix or uterus, or directly into the tissue (interstitial) via applicators fitted with specialized needles.

Delivery of brachytherapy may be carried out at different dose rates: a high dose rate (**HDR**: a high dose over a short time), pulsed dose rate (**PDR**: dose delivered in pulses over about a day) or low dose rate (**LDR**: dose delivered over a period of 2–3 days).[17]

Whilst LDR brachytherapy has been successfully utilized for decades, **HDR brachytherapy is fast becoming the technique of choice due to a number of inherent advantages of rapidly delivering radiation.** These include greater precision, lower hospitalization costs, and greater patient convenience.[17]

# Leading innovation in radiotherapy

Brachytherapy delivers highly conformal, effective treatment. Due to the intrinsic nature of brachytherapy, the intensity of radiation decreases rapidly the further it is from the source. High doses can be delivered to target **tissues with surrounding healthy tissues receiving as minimal a dose as possible,** therefore limiting toxicity.[18]

The technology utilized is constantly evolving. These advances build on the established principles of brachytherapy to facilitate even **greater levels of precision**, further improving efficacy and toxicity outcomes and delivering highly individualized patient care.[12]

## Innovations in brachytherapy imaging and planning

In recent years advances in imaging and computerized planning have allowed improved dose specification to target tissues.

The use of X ray and computed tomography (CT) for treatment planning have already proven invaluable in terms of clinical outcomes.[19]

The introduction of so-called 'volume' based techniques, using magnetic resonance imaging (MRI) or CT and MRI for treatment planning and guidance allow even greater precision in defining the exact amount of irradiation to be delivered to specific volumes of target tissue (Figure 2). Importantly, this also ensures that the exposure of potentially damaging levels of radiation to nearby healthy structures and organs, like the bladder and rectum, is reduced.[20]

## Image guided adaptive brachytherapy (IGABT)

IGABT uses MRI before and during treatment to enable 4D treatment planning (i.e. 3D volume-based visualization plus accounting for changes occurring between treatment sessions, such as tumor shrinkage or changes in the surrounding tissues with time). **This results in even greater levels of precision**.[21]

A study in cervical cancer showed that, compared to image-guided IMRT or IMPT techniques, brachytherapy can provide excellent dose distribution and reduced dose volumes to surrounding tissue.[18]

## Innovations in applicator design

**Applicator design is continually progressing, including the development of so-called combined intracavitary and interstitial techniques.** The 'Vienna ring' applicator (Figure 3), for example, integrates an applicator delivering radiation within the uterine cavity as well as specially adapted needles which are placed directly in the affected tissues. Use of such applicators allows the distribution of the radiation to be finely tuned to match and 'cover' the form of the tumor being treated.[22] This extends the coverage of the treatment beyond that of conventional applicators and allows more advanced tumors to be treated.

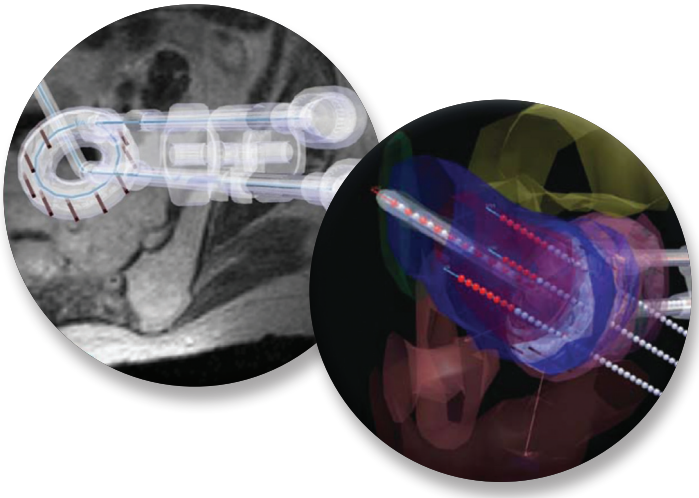

**Figure 2**. MRI based computer treatment planning

**Figure 3**. The 'Vienna ring' applicator combines interstitial and intracavitary techniques

# Brachytherapy in cervical cancer treatment

## Efficacy

**Brachytherapy is part of the standard of care for treating cervical cancer.** It is the standard treatment for bulky (stage IB2) or locally advanced disease (stages IIA–IVA), typically in combination with EBRT and chemotherapy. Both LDR and HDR brachytherapy are used to treat cervical cancer. When comparing these two approaches for Stage I–III disease, no significant differences in overall survival and local recurrence have been found between LDR and HDR, with the advantage of shorter treatment times and greater convenience with HDR brachytherapy.[10,23]

In early disease, brachytherapy provides **comparable long-term efficacy to surgery** and is a viable alternative. A comparative study showed a complete response rate of 85% for LDR brachytherapy versus 55% for surgery (both were combined with EBRT-chemotherapy). Both groups had projected 5-year survival rates of 78% showing that in the long-term, **brachytherapy is equal to surgery in terms of survival**.[8]

In both locally advanced and advanced stages, **brachytherapy combined with EBRT provides excellent long-term survival rates and represents the standard of treatment for these stages.** Furthermore it has been demonstrated that this **combination provides superior patient outcomes than when EBRT is used alone**.[6, 24]

The effectiveness of brachytherapy for cervical cancer **has been further aided by the use of advanced brachytherapy techniques**. One study (Figure 4) showed that for tumors >5cm, the introduction of 3D MRI based brachytherapy, with greater control of dose to specific volumes, along with use of interstitial techniques in the years 2001–2003 led to an increase in the probability of achieving long-term overall (OS) and cancer specific survival (CSS) compared to the more classic techniques used between 1998–2000.[21]

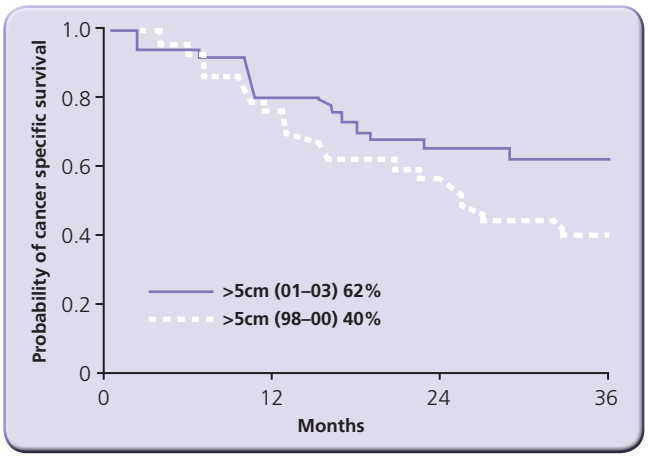


**Figure 4**. Increased probability of cancer specific survival with the introduction of IGABT[20†]

## Side effects and quality of life

**Precision placement of the radiation dose to the target tissue minimizes gastrointestinal (GI) and bladder toxicity, allowing patients to return to everyday life quickly.**

***Gastrointestinal and bladder function:*** There is a **low incidence of severe side effects affecting the GI system and the bladder** following brachytherapy, with no differences in terms of incidence of events between HDR and LDR brachytherapy. For the majority, complications are of a low grade and do not require treatment.[10]

***Vaginal adverse events:*** Severe vaginal toxicity (including mucous membrane inflammation, atrophy and fibrosis) is rare following brachytherapy. Low-grade acute and long-term vaginal toxicity occurs in less than a third of patients.[25]

***Quality of life:*** Due to the **low incidence of side effects**, brachytherapy minimizes impact on quality of life. Additionally, the short outpatient treatment for HDR brachytherapy means **minimal disruption to patients' everyday lives**. When used as an alternative to surgery, brachytherapy offers shorter recovery times with fewer complications.[10]

# Brachytherapy in endometrial cancer treatment

## Efficacy

**Brachytherapy provides excellent cancer cure rates** for both early and intermediate stage endometrial cancer, with **comparable efficacy to EBRT. Low recurrence rates (3.4%)** are demonstrated in patients with early stage disease. HDR brachytherapy is becoming the **standard of care** for patients following surgery in these disease stages.[26]

Brachytherapy has shown **comparable efficacy to EBRT in high-intermediate risk patients**. The PORTEC-2 study reported similar 5-year vaginal recurrence rates of 1.8% for HDR/LDR brachytherapy and 1.6% for EBRT. Overall survival or progression-free survival rates were also similar (Figure 5).[7]

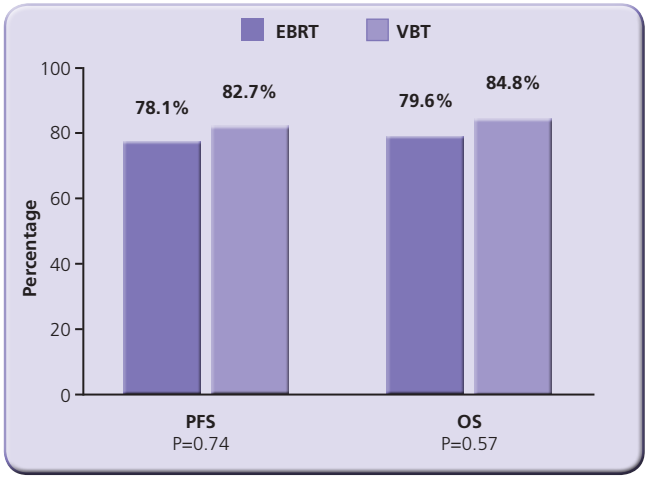


**Figure 5**. Estimated progression-free survival (PFS) and overall survival (OS) at 5 years post-treatment (Adapted from Nout *et al,* 2010)[7]

HDR brachytherapy, with or without EBRT, is a **highly efficacious treatment when surgery is not an option.** A recent investigation of Stage I–III patients showed local recurrence occurring in only 6.1% of patients, with a 3-year overall survival rate of 83%.[27]

> ***"VBT should be the adjuvant treatment of choice for patients with endometrial carcinoma of high-intermediate risk."***[7]

## Side effects and quality of life

**With comparable efficacy between different treatment options, other elements such as side effects and impact on patients' quality of life become important treatment considerations. As brachytherapy minimizes radiation doses to surrounding healthy tissues, a benefit of brachytherapy for patients is reduced side effects and a better quality of life.**

***Quality of life:*** Factors, such as social functioning, are **significantly better** following brachytherapy.[11]

***Gastrointestinal function:*** **Rates of GI toxicity, for example diarrhea, following brachytherapy are low.** This translates to **less disruption to everyday life** in both the short and long-term (Figure 6).[11]

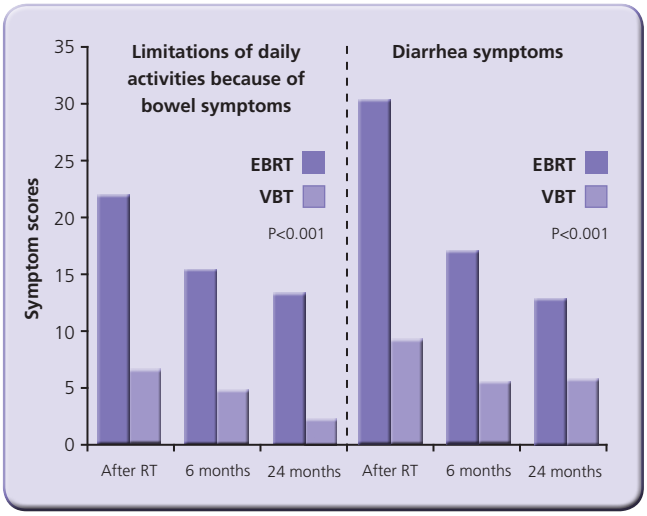


**Figure 6**. Limitations of daily activities and diarrhea symptoms following EBRT and VBT (Adapted from Nout *et al*, 2009)[11]

***Urinogenital side effects:*** **Urinogenital side effects are generally low, and of a low grade**, resulting in minimal impact on quality of life.[28]

***Sexual activity:*** Impact on sexual activity may be a worry for women undergoing brachytherapy. However the PORTEC-2 trial found **significant increases in patient-reported sexual interest and activity** compared to pre-therapy levels.[11]

## Summary

Brachytherapy is part of the **standard of care for treating cervical and endometrial cancers.** Utilizing techniques established and refined over several decades, brachytherapy has proven to be effective both as a stand-alone treatment and in combination with EBRT.

Advances in gynecological brachytherapy imaging, treatment planning and applicator design facilitate even **greater precision** in dose delivery and ability to limit harmful radiation to surrounding healthy tissues. These are enabling brachytherapy to be **utilized in the widest possible range of complex gynecological cancers.**

**Excellent efficacy outcomes combined with reduced risk of side effects, short outpatient treatment times and better quality of life makes brachytherapy a patient-centered treatment choice.**

**Shorter treatment times also lower the costs involved in brachytherapy,** taking patients and staff from the inpatient to the outpatient setting.

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**For further information on brachytherapy for gynecological cancers, consult the following resources:**

**Speak to colleagues who have successfully integrated brachytherapy into their practice**

**ESTRO** (European Society for Therapeutic Radiology and Oncology)
www.estro.org

**ASTRO** (American Society for Therapeutic Radiology and Oncology)
**www.astro.org**

**GEC-ESTRO** (Groupe Européen de Curiethérapie and the European Society for Therapeutic Radiology and Oncology
www.estro.org/about/Pages/GEC-ESTRO.aspx

**ABS** (American Brachytherapy Society
www.americanbrachytherapy.org

**NCCN** (National Comprehensive Cancer Network)
www.nccn.org



# Brachytherapy:

## *The* precise answer for tackling gynecological cancers

Reasons to consider brachytherapy in gynecological cancer management

- Demonstrated efficacy
- Precision radiotherapy
- Minimized toxicity
- Patient-centered
- Cost-effective
- State-of-the-art

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