REVIEW ARTICLE UDK: 616.14-006.6-089.849-089.5

INTRAVAGINAL BRACHYTHERAPY SUPPORTED BY LOCAL ANAESTHESIA IN THE TREATMENT OF ENDOMETRIAL CANCER – SINGLE INSTITUTIONAL EXPERIENCE

Klisarovska V[1], Smichkoska S[1], Stojkovski I[1], Dzundeva J[1], Bojoski P[1], Hristovska E[1]
[1] University Clinic of Radiotherapy and Oncology, Skopje, Republic of North Macedonia

ABSTRACT

Intravaginal brachytherapy in endometrial cancer is an inevitable part of the treatment. In the early stages of the disease, it significantly reduces the risk of local recurrence in the vaginal cuff with low rates of late toxicity. In the advanced stages, it provides palliative control usually with a hemostyptic effect. Brachytherapy may be the only postoperative treatment – monotherapy, or as a boost following the external beam radiotherapy, depending on many prognostic factors. Placing the vaginal applicator deep into the vagina is certainly an uncomfortable feeling, combined with pain, anxiety and discomfort. Local anaesthesia helps in reducing the painful sensations, gives adequate relaxation, but more importantly provides a quality insight into the condition of the vagina, and thus a successful application. Through our experience with the local vaginal anaesthesia with lidocaine 2% gel, we want to emphasize that intravaginal brachytherapy, supported by local anaesthesia, regardless of the degree of pain relief is directly related to successful treatment.

Key Words: *anaesthesia, analgesia, endometrial cancer, intravaginal brachytherapy.*

Brachytherapy role

Endometrial cancer is one of the most common type of malignancy in women around the word. Bourdais of the GLOBOCAN cancer statistics, estimated that 382,069 new cases and 89,929 deaths worldwide in 2018 are attributed to endometrial cancer. Futhermore, this type of cancer was reported as the the second most common and the fourth leading cause of death in respect to the gynecological cancer types in 2018 (1). In North Macedonia, the number of newly diagnosed women with uterine cancer is 192 cases per 100,000 population and mortality is 37 deaths per 100,000 population.

Primary management of endometrial cancer is consisted in surgical removal of the uterus (total abdominal hysterectomy) and bilateral salpingo-oophorectomy. Adjuvant radiation therapy may be recommended when higher stage of the disease is present, with proved increased depth of myometrial invasion, concomitant lymphovascular space invasion, increased age, increased tumor size, histology, lymph node positivity and other adverse risk factors (2-6). Recurrence rate of the tumors is 10-20% and out of these rates (80-90%) will recur within three years (7). Treatment of recurrences may be a real challenge. If local vaginal recurrences are diagnosed early are curable while pelvic and distant recurrences have a poor prognosis and outcome. Furthermore, in these patient's chemotherapy and/or external beam radiotherapy (EBRT) may decreases the risk of locoregional failure. However, the toxicity over all will be increased.

Local recurrences are most often present in the vagina so vaginal brachytherapy (VBT) rather than EBRT is a good choice for patients since it decreases this risk of recurrence rate with minimal toxicity present (6). VBT treatment for early stage endometrial cancer should provide sterilization of the vaginal incision from possible postoperative microscopic spread of the disease (8,9). In patients who have not had surgery (usually due to internal comorbidity) or in patients who cannot have EBRT (usually due to obesity), VBT plays a key role in treatment. Therefore, VBT has become an inevitable part nowadays in the treatment of endometrial cancer.

Brachytherapy presents a form of internal radiation treatment. In this type of treatment radioactive sources are placed direct on or into cancer tissues, or on tumor bed. It this way extremely high dose of radiation are allowed to be received by the tumor and the sparing of the organs at risk is relative. VBT compared to EBRT, delivers a conformal dose to the vagina and small spread to the surrounding tissues. This is certainly allowed by its anatomy and placement.

The vagina is a **fibromuscular tube** with anterior and posterior walls. These walls are collapsed in contact with one another. At the upper end vagina is surrounding the cervix where it creates two domes, the an anterior and a posterior one. The length of the vagina is different from woman to woman. Due to the presence of the cervix in the front wall of the vagina and there is difference in length between the front wall (7.5 cm long) and the back wall (approximately 9 cm long).

Intravaginal brachytherapy is usually adjuvant after a hysterectomy. It is realized with a vaginal applicator, through which the required irradiation dose will be realized in the region of the vaginal cuff on the upper vaginal area, an area at high risk for recurrence (10). Therefore, VBT is an important part of the treatment of endometrial cancer, either as a single treatment, or in combination with EBRT and/or chemotherapy in advanced stages of disease (11, 12). Apart from the benefit, it must be emphasized that its side effects are insignificant and easy to manage, due to the specific possibility of brachytherapy for high dose loading of the target volume, and almost complete protection of healthy structures. It has been proven toxicity rates shown by the bladder, rectum, bowel, bone, or bone marrow are quite low. However primary risk of toxicity with VBT is forwarded to the proximal vagina which may result in vaginal atrophy, stenosis, and/or shorten vaginal length.

Intravaginal brachytherapy modalities

VBT technique can be realized with many different applicators. A vaginal mold applicator has been studied with the potential benefit of customization of the applicator to the patient's vaginal anatomy with decreased air pockets and potentially improved dosimetry (13) (Image 1). There is also a set of vaginal cylinders that contain applicators with equal length of 14 cm, but with different diameter in the range of 2 to 3.5 cm (Image 2). Another set is the set of segmented

vaginal applicators that allow a difference in lengths (Image 3). However, the vaginal cylinder is a smooth, plastic cylinder, with one central channel or more channels distributed across the diameter of the applicator, through which the radioactive source can move and create the radiation dose shaping around the target volume.

Most commonly used applicator is a single channel vaginal cylinder. This applicator is the simplest to plan. It treats the vagina circumferentially and equally to the depth of dose specification. Single channel vaginal cylinder delivers decreased dose at depth superior to the vaginal apex as a result of anisotropy. Multi-channel vaginal cylinders show advantage of customizing dose to either deliver asymmetric doses or avoid adjacent normal structures. The multi-channel cylinder has been shown to decrease dose to the bladder and rectum, but at the expense of increased vaginal mucosa dose. Patients with large lesions or those that are >5mm thick may benefit from a multi-channel cylinder, but they may still be difficult to be adequately treated without delivering excess dose to the vaginal surface (6,8).

Image 1. *Vaginal mold applicators*

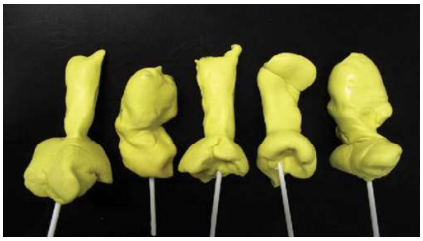


Image 2. *Vaginal cylinder applicator set*

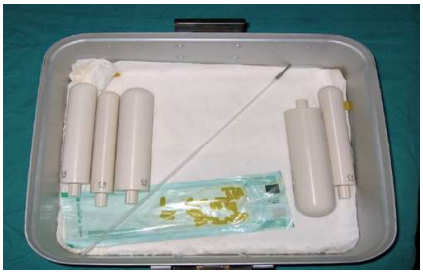
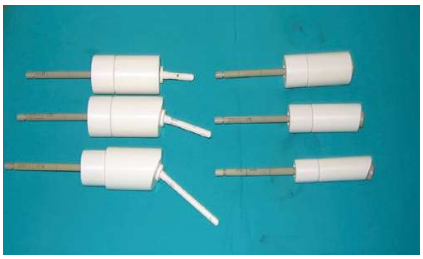


Image 3. *Segmented vaginal applicator set*



VBT procedure usually requires patient's cooperation and immobilization which can only be achieved when the patient is comfortable and relatively free from pain. On the contrary, insertion may not be properly done and this may result in poor distribution of dose and complications arising from giving too much radiation dose to the organ at risk (rectum and bladder) and inadequate dose to the tumor itself.

Type of vaginal pain

Vagina is innervated predominantly from the autonomic nervous system. Parasympathetic and sympathetic nerves arise from the **uterovaginal nerve plexus** (in turn a subsidiary of the inferior hypogastric plexus). Inferior 1/5 of the vagina receives somatic innervation. This is throught the pudendal nerve, the **deep perineal nerve**. Because the pudendal nerve carries motor and sensory fibers that innervate the pelvic muscles, a pudendal nerve block relieves pain.

The presence of a vaginal applicator deep in the vagina triggers different sensations in patients, depending on their sensitivity – pain threshold. That stimulates sympathetic autonomic afferents which enter the spinal cord at the T10-L1 level. This produces poorly localized, central, lower abdominal pain, sometimes associated to nausea and vomiting. Distension of the upper vagina stimulates parasympathetic autonomic afferents from the pelvic splanchnic nerves of S2-4 to cause lower back pain. Distension of the lower parts of vagina through the labia stimulates somatic afferents via the pudendal nerves of S2-4 (14).

The optimal anaesthetic technique has not been recognized by published data. In practice, local anaesthesia is preferred. Lidocaine is a commonly used local anesthetic for vaginal procedures. The aim is to provide good analgesia (painlessness) and muscle relaxation. More importantly, it allows better placement of the applicators. Topical or local anaesthesia is used by radiotherapists.

Anaestesia modalities

Anaesthesia in brachytherapy does not have a single prescribed recommendation, it varies from one center to another, depending on the technique of application. Almost all anaesthesia procedures are used. Uterovaginal applications are invasive, so they usually use general, epidural, or spinal anaesthesia. In intravaginal applications, as less invasive, local anaesthesia is an excellent choice and is increasingly being implemented.

Lim et al, showed the complications related to different methods of anaesthesia (general anaesthesia, topical anaesthesia and sedation, paracervical nerve block and conscious sedation) using the Common Toxicity Criteria (15). General anaesthesia has significantly more complications than other methods, spinal or topical anaesthesia (16).

According to Elumelu et al (17) local vaginal anaesthesia with 10% xylocaine spray can decrease the degree of pain during HDR intracavitary brachytherapy with no expected major side effects.

Some centers use a vaginal pack with lidocaine 2% gel, which is placed about 15 minutes before starting the procedure. Significant pain control is achieved during the procedure, but an additional comfort period is also noted after the procedure (18).

Generally, local lidocaine anaesthesia is considered easy to administer, comfortable, and low-priced which makes it affordable.

Single institutional experience

The Brachytherapy Department within the University Clinic of Radiotherapy and Oncology, Skopje, the only one of its kind in our country, is also a regional center, because in addition to domestic, also treats patients from neighboring countries, thanks to the technical and staff support. Starting from 2005 until today, an average of 250 intravaginal applications are realized per year, the most of which (about 75%) are postoperative, and the remaining 25% are part of the definitive treatment of endometrial carcinoma. Through our clinical experience, including excellent response and patient monitoring, we want to highlight the importance of intravaginal brachytherapy in the treatment of endometrial cancer.

The aim is to point up that VBT supported by local anaesthesia, regardless of the degree of pain relief, even with minimal pain relief, is directly related to successful application and an optimum brachytherapy treatment effect.

Selecting patients

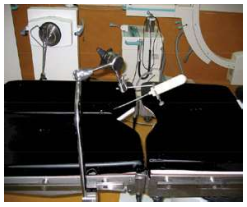
All patients requiring intravaginal brachytherapy are candidates for application under local anaesthetic. These are patients in postoperative setting (because of shortened vagina), non-operative patients (because of local active disease, vaginal stenosis) or patients after EBRT (because of radiation fibrosis).

Intravaginal application technique

The treatment is carried out in a dedicated brachytherapy room (Image 4). The procedure is an aseptic one. It begins with catheterization of the bladder, Foley's catheter is inserted, filled with 7 ccm contrast and fixed against the bladder neck, necessary for visualization of the organ at risk. An examination under the speculum makes an assessment of the local finding in the vagina, its length and the possibility of stretching. The choice of vaginal applicator depends on it. We use a single channel vaginal applicator. After the betadine wash, lidocaine 2% gel is smeared in the vagina, which after about 5 minutes provides easy pain relief in the vagina and easier sliding of the vaginal cylinder deep into the vagina. The position of the applicator is fixed with a *universal Varian applicator clamping device (Image 5)*. The vaginal applicator is CT/MRI compatible. Only for 2D planning rectal marker is placed deeply in the rectum to visualize it (Image 6). In patients with active hemorrhoidal problems, local anaesthesia is also used for a more comfortable placement of the rectal marker (by applying a gel on the tip of the marker). After that, all patients undergo 2D or 3D – CT simulation and return to the operating room – brachytherapy bunker, without fear of applicator displacement, because of special transport tabletop.

Image 4. *Brachytherapy treatment room*

Image 5. *Fixed position of the applicator with a universal Varian applicator clamping device*



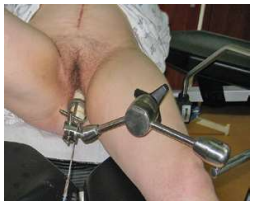
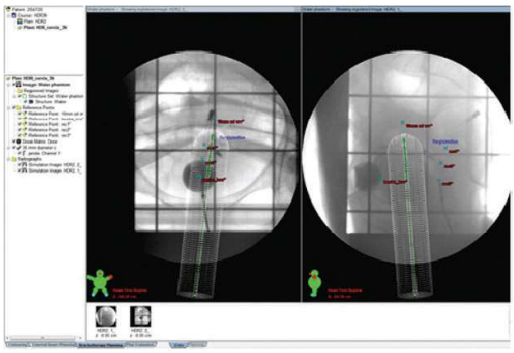


Image 6. *Orthographic images with vaginal applicator*



Adjuvant intravaginal brachytherapy (postoperatively or after EBRT) is administered via 1 fraction, with a prescribed dose of 7 Gy, at 5 mm from the tip of the applicator. As part of the definitive treatment (non-operative patients or inoperable active disease) 3 fractions are realized, once a week, with a prescribed daily dose of 7 Gy, at 10 mm from the tip of the applicator, until realization of a total tumor dose of 21 Gy.

When dosimetric planning is completed, we deliver HDR brachytherapy using a remote after loader device (Varian, GammaMedPlus) with Iridium 192. Once the prescribed dose is delivered, we remove the applicator and the Foley catheter. The entire procedure is usually in the outpatient setting.

Depending on the local finding (shortened vagina, presence of surgical incision, pain threshold), patients may be prepared intravenously before treatment with analgesics and muscle relaxants.

Our experience with VBT supported by local anesthesia has so far shown no impairment of patient's safety, no adverse effects during the procedure or any periprocedural morbidities or complications. Acute side effects are very rare. If they occur, first-degree cystitis and proctitis (according to Common Terminology Criteria for Adverse Events), are the most common and are easily managed and completely acquired. Late side effects include vaginal dryness and stenosis, which are solved by vaginal dilators. We haven't registered mortality as a result of this treatment. The follow-up of patients is always adjusted according to the overall treatment, not specifically for brachytherapy.

It must be noted that this report has few limitations. Our experience is associated exclusively to the use of lidocaine 2% gel, therefore without the possibility of comparison with other anaesthetics. We don't evaluate the patient's emotions, such as fear, anxiety, pain and distress. The reduction of pain clearly provides better relaxation of the patient, which in the quality intravaginal application is the most important segment. Our future plans are to prove the above objectively by scoring the pain, through the appropriate pain relief scales.

Conclusion

Intravaginal brachytherapy in endometrial cancer is an inevitable part of treatment. In the early stages of the disease, it has a curative effect that provides long and quality life and in the advanced stages, it provides palliative control usually with a hemostyptic effect. The maximum benefit is directly dependent on the proper placement of the vaginal cylinder, where the local anaesthesia has the significant role. Lidocaine gel alleviates patient discomfort, thus providing clear insight into the local status and proper placement of the vaginal applicator, with a fully regulated safety profile, without any side effects.

References

1. Bray F, Ferlay J, Soerjomataram I, et al. Global Cancer Statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. CA Cancer J Clin 2018; 68:394-424.
2. Aalders J, Abeler V, Kolstad P, et al. Postoperative external irradiation and prognostic parameters in stage I endometrial carcinoma: clinical and histopathologic study of 540 patients. Obstet Gynecol 1980; 56:419 – 427.
3. Creasman WT, Morrow CP, Bundy BN, et al. Surgical pathologic spread patterns of endometrial cancer. A Gynecologic Oncology Group Study. Cancer 1987; 60:2035 – 2041.
4. Creutzberg CL, van Putten WL, Koper PC, et al. Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. PORTEC Study Group. PostOperative Radiation Therapy in Endometrial Carcinoma. Lancet 2000; 355:1404 – 1411.
5. Keys HM, Roberts JA, Brunetto VL, et al. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group study. Gynecol Oncol 2004; 92:744 – 751.
6. Nout RA, Smit VT, Putter H, et al. Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): an open-label, non-inferiority, randomised trial. Lancet 2010; 375:816 – 823.
7. Jereczek-Fossa B, Badizo A, Jassem J. Recurrent endometrial cancer after surgery alone: results of salvage radiotherapy. Int J Radiat Oncol Biol Phys 2000; 48:405-413.
8. Harkenrider MM, Block AM, Alektiar KM, et al. American Brachytherapy Task Group Report: Adjuvant vaginal brachytherapy for early-stage endometrial cancer: A comprehensive review. Brachytherapy 2017; 16:95-108.
9. Lancellotta V, Felice F, Vicenzi L, et al. The role of vaginal brachytherapy in stage I endometrial serous cancer: a systematic review. J Contemp Brachytherapy 2020; 12:61-66.
10. Harkenrider MM, Block AM, Zaid A, et al. The role of vaginal cuff brachytherapy in endometrial cancer. Gynecol Oncol 2015; 136:365-372.
11. Sabater S, Andres I, Lopez-Honrubia V, et al. Vaginal cuff brachytherapy in endometrial cancer – a technically easy treatment? Cancer Manag Res 2017; 9:351-362.

12. Craig MacLeod, Allan Fowler, Peter Duval, et al. High-dose-rate brachytherapy alone post-hysterectomy for endometrial cancer. Int J Radiat Oncol Biol Phys 1998; 42:1033-1039.
13. El Khoury C, Dumas I, Tailleur A, et al. Adjuvant brachytherapy for endometrial cancer: advantages of the vaginal mold technique. Brachytherapy 2015; 14:51 – 55.
14. Kwekkeboom KL, Dendaas NR, Straub M, et al. Patterns of pain and distress during high-dose-rate intracavitary brachytherapy for cervical cancer. J Support Oncol 2009; 7:108 – 14.
15. Lim KH, Lu JJ, Wynne CJ, et al. A study of complications arising from different methods of anaesthesia used in high-dose-rate brachytherapy for cervical cancer. Am J Clin Oncol 2004; 27:449 – 451.
16. Benrath J, Kozek-Langenecker S, Hupfl M, et al. Anaesthesia for brachytherapy – 5 1/2 yr of experience in 1622 procedures. Br J Anaesth 2006; 96:195-200.
17. Elumelu-Kupoluyi TN, Abdus-Salam AA, Eriba LO. Topical anaesthesia for pain relief during high dose rate brachytherapy for carcinoma of the cervix. West Afr J Radiol 2015; 22:10-4.
18. Roessler B, Six LM, Gustorff B. Anaesthesia for brachytherapy. Curr Opin Anaesthesiol 2008; 21:514-8.

 UDK: 616.98:579.834]-036.21:614.253.5

COVID-19: CHALLENGES AND OPPORTUNITIES FOR NURSING CARE IN NON-COVID, INTENSIVE CARE UNIT (ICU)

What is it like being an intensive care nurse on the front lines during the COVID-19 pandemic?

The Covid-19 pandemic is placing an unprecedented strain on the nation's health care facilities and revealing many underlining weaknesses that exist in the health care system. The policies, processes and capacities of individual health units for safe and timely patient care, emergency preparedness, resources allocation and intra and inter-sectional collaboration, are the key determinants for a successful response to the pandemic. Preparing the ICU is an integral part of any pandemic response.

The University Clinic for Surgical Diseases "St. Naum Ohridski" is an established healthcare facility in our country's health system. Intensive Care Unit (ICU) in the clinic of surgery is the multispecialty medical care center for critically ill patients who require surgery, such as a motor vehicle accident or other trauma, accident victims. It provides care to patients suffering from brain injuries and to patients recovering from complex surgeries that need frequently nursing care. In this letter, I would like to discuss some of the key principles and strategies for ICU preparedness, and our experiences in such conditions.

Since the beginning of the pandemic until now (end of August 2020), the ICU at the University clinic for surgical diseases "St. Naum Ohridski", Skopje, has been following all the protocols and guidelines according to world standards and WHO recommendations.

Firstly, the clinic has set up a Coordinating Commission to deal with global coronavirus conditions. Generally, ICU nurses provide the most of the direct care to the critically ill patients with life threatening conditions, they develop and implement nursing care plans, and maintain medical records. They use their advanced skills to care for patients who are critically ill and at high risk with life-threatening health problems. ICU nurses must be physically, mentally, and emotionally strong in order to be able to work with seriously ill patients. Wearing protective equipment, visors, masks (surgical and N95), surgical hats, disposable gowns, tins, as well as continuously care for hand disinfection, have been mandatory for all medical staff, especially nurses.

According to the protocols, the first action was based on measuring body temperature at the entrance of the hospital, where triage is performed for the degree of urgency. Any patient who had a fever (above 37 C degrees) was considered suspicious and was referred to the Covid Center for further treatment. An area is defined in which an individual is evaluated and screened using the case definition; if the person becomes a suspected case, the nurse should refer to COVID-19 protocol. Isolation: If the case definition is met, the patient should immediately be given a mask and directed to a separate area (an isolation room, if available). At least 1 meter distance should be kept between suspected patients and other patients. Acuity-based triage is the standard method of sorting patients in the medical setting. This is used as the basis for identifying patients who require immediate medical intervention, patients who can safely wait, or patients who may need