Original paper

Vaginal cuff brachytherapy practice in endometrial cancer patients: a report from the Turkish Oncology Group

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Abstract

Purpose: The American Brachytherapy Association is attempting to develop standards for delivering brachytherapy, although differences in practice have been reported in the literature. This study evaluated vaginal cuff brachytherapy (VBT) practice and quality of life-related recommendations among Turkish radiation oncologists.

Material and methods: A nationwide web-based 17-item survey was distributed to the members of the Turkish Society for Radiation Oncology. These members received e-mail notifications, and a link was posted on the Turkish Society for Radiation Oncology internet site to solicit voluntary responses The survey addressed the simulation processes, target volume, prescribed dose, delivery schedules, and recommendations related to vaginal side effects.

Results: Fifty-seven radiation oncologists responded to the survey. The most used dose fraction schemes for adjuvant VBT were 7 Gy × 3 fractions (30%), 5.5 Gy × 5 fractions (26%), and 6 Gy × 5 fractions (28%). The preferred VBT scheme was 5 Gy × 3 fractions (50%) when the external beam radiotherapy (EBRT) dose was 45 Gy external radiotherapy, while the preferred schemes were 6 Gy × 3 fractions (30%) or 5 Gy × 3 fractions (32%) when the external radiotherapy dose was increased to 50.4 Gy. One-half of the respondents delivered VBT twice a week, and the dose was prescribed to 0.5 cm from vaginal mucosa by 86% of the respondents. There was no common definition for the dose prescription length, which was defined as 3 cm from the vaginal cuff in 33% of responses and as 4 cm in 35% of responses. For serous and clear cell histological types, 38% of the respondents targeted "full cylinder length". To prevent vaginal side effects, 78% of the respondents recommended using a vaginal dilator and/or sexual intercourse after VBT.

Conclusions: This survey revealed variations in the clinical practice of VBT among Turkish radiation oncologists, which suggests that standardization is necessary.

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Key words: brachytherapy, vaginal cuff, experience, survey.

Purpose

Endometrial cancer (EC) is the most common gynecological malignancy. In the era of comprehensive pelvic and paraaortic lymphadenectomy, vaginal cuff brachytherapy (VBT) provides high local control rates with minimal toxicity for early-stage disease [1]. PORTEC-2 trial revealed that VBT alone could be a less toxic alternative to external radiotherapy (RT) for intermediate- to high-risk EC [2]. Furthermore, analysis of data from the surveillance, epidemiology, and end results database revealed a trend toward an increased use of VBT alone for patients with early-stage EC [3]. However, there is a significant benefit associated with combining VBT and pelvic RT for select patients, especially those with advanced-stage disease [4].

The American Brachytherapy Society (ABS) has published a guideline with recommendations and indications regarding the use of VBT for patients with EC [5]. In the early 2000s, that report highlighted the use of high-dose-rate (HDR) brachytherapy and eventually helped standardize the use of brachytherapy, with updates published in 2012 [5, 6]. Based on these guidelines, American radiation oncologists and ABS members were surveyed in 2005 and 2015 regarding their use of post-operative VBT [7-9]. The survey results showed some variability,

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although the use of VBT was generally aligned with the ABS recommendations [7, 8, 10]. Moreover, an Italian survey was performed in 2016 to examine the current practice of VBT and external beam RT based on the latest technological developments, such as image-guided adaptive brachytherapy and RT [11]. Therefore, we performed a survey to evaluate the use of adjuvant VBT for patients with EC in Turkey.

Material and methods

During January 2017, four experienced radiation oncologists (YB, FY, ZO, and CO) who are specialized in brachytherapy, developed a survey as a part of the Gynecological Cancer Group of the Turkish Society of Oncology (TOG) (Appendix). The survey consisted of 17 questions regarding various parameters, including treatment planning and post-treatment follow-up. The first section addressed treatment preparation and simulation processes, the second section considered target volume delineation techniques, prescribed doses, and delivery schedules, while the third section addressed precautions and recommendations regarding vaginal side effects.

At present, there are 30 RT centers in Turkey, with an equipment needed to perform intracavitary HDR brachytherapy. The survey was created using an online survey program (www.SurveyMonkey.com), which generated a web-based link to the survey. The survey link and an invitation to voluntarily participate were emailed to the 66 members of the gynecological oncology subgroup, and the invitation was also posted on the website of the Turkish Society for Radiation Oncology (TROD). The survey was open between January 2nd and February 12th, 2018, and took approximately 4 min to complete.

Results

VBT preparation and simulation

Among the 66 members of the TROD gynecological oncology sub-group, 57 radiation oncologists completed the survey (response rate, 86%). The first section of the survey showed that computed tomography (CT)-based simulation was used for only the first fraction by 65% of the respondents, while 21% of respondents preferred CT-based planning for each fraction (Table 1). Approximately 47% of respondents used a urinary catheter to fill the bladder to some degree for each faction, while 35% of respondents did not use urinary catheters. Furthermore, 42% of respondents did not recommend completely filling the bladder during VBT planning and delivery. One-half of the respondents reported using enema at every fraction to provide consistent rectal doses.

Table 1. The preparation and simulation processes for vaginal cuff brachytherapy

Procedures	All fractions	First fraction	Not recommended
Urinary catheter	47%	18%	35%
Bowel preparation	51%	–	49%
CT-based simulation	21%	65%	14%

Bowel preparation: any diet intervention or enema use before each application

Dose prescription and delivery schedules

The prescribed doses were stratified according to the use of VBT alone or VBT with external RT. The most common schemes for VBT alone were 7 Gy × 3 fractions (30%), 5.5 Gy × 5 fractions (26%), and 6 Gy × 5 fractions

Table 2. Vaginal cuff brachytherapy dose and fractionation, and treated volumes for vaginal cuff brachytherapy. The questions related to preferred fraction schedules were asked in multiple choice design to assess whether more than one schedule could be in standard clinical use

Parameter (No. of participants/No. of answers)	%
Vaginal cuff BRT only (n = 57/66)*	116*
7 Gy × 3 fractions	30
5.5 Gy × 5 fractions	26
6 Gy × 5 fractions	28
5 Gy × 5 fractions	16
7 Gy × 4 fractions	12
Other	4
45 Gy external RT + vaginal cuff BRT (n = 56/65)*	116*
6 Gy × 3 fractions	34
5 Gy × 3 fractions	50
7 Gy × 3 fractions	21
5 Gy × 4 fractions	9
6 Gy × 2 fractions	2
Other	0
50.4 Gy external RT + vaginal cuff BRT (n = 56/60)*	107*
5 Gy × 3 fractions	32
6 Gy × 3 fractions	30
4 Gy × 3 fractions	18
6 Gy × 2 fractions	16
4 Gy × 4 fractions	4
Other	7
Target volume for adenocarcinoma (n = 57)	100+
First 4 cm cranially	35
First 3 cm cranially	33
Apical 1/3 of vagina	19
Entire cylinder	13
Target volume for serous or clear cell histology (n = 57)	100+
First 4 cm	35
First 3 cm	11
Entire cylinder	38
Other	16

** The participants could indicate more than one answer according to their clinical practice for the first 3 questions regarding dose schedules. Based on this multiple answers option, even 57 radiation oncologist answered the survey, more than 65 answers were notes in the results section; + these questions were designed as a single choice, so the participants could choose only the most suitable answer*

Table 3. Treatment schedules and post-treatment recommendations

Parameter (n = 57)	%
Fraction sequency of application	
Everyday	16
Every other days	23
Every two days (twice in a week)	53
Other	8
Dose prescription	
Surface of vaginal mucosa	11
At 0.5 cm	86
Other	3
Timing of brachytherapy and chemotherapy	
Before chemotherapy	25
Between chemotherapy cycles	30
After chemotherapy	45
Timing for sexual intercourse	
Immediately after treatment	5
1 week after treatment	11
3 week after treatment	40
6 week after treatment	44
Other	0
Vaginal dilatators or sexual intercourse	
Once weekly	78
No	22
Estrogen-based vaginal gel	
Yes	68
No	32

(28%) (Table 2). When the VBT was combined with external pelvic RT (45 Gy in 25 fractions), the most common VBT schemes were 5 Gy × 3 fractions (50%), 6 Gy × 3 fractions (34%), and 7 Gy × 3 fractions (21%). When the VBT was combined with higher dose external RT (50.4 Gy in 28 fractions), the most common VBT schemes were 5 Gy × 3 fractions (32%), 6 Gy × 3 fractions (30%), and 4 Gy × 3 fractions (18%). Approximately one-half of the respondents (52%) reported using two applications per week. Majority of the respondents (86%) reported that the dose was prescribed to 0.5 cm from the vaginal mucosa.

The VBT target volume was defined as the first 3 cm from the vaginal cuff in 33% of responses, the first 4 cm in 35% of answers, and the entire cylinder in 13% of responses. Furthermore, 19% of the respondents preferred treating the apical 1/3rd of the vaginal mucosa. A change in the treated volume was made by 38% of the respondents for patients with serous or clear cell histology. Most of the respondents (93%) agreed that brachytherapy should be performed after external RT for cases involving serous or clear cell histology. None of the respondents reported changing their dose preference according to histology. When VBT was combined with chemotherapy, 45% of the participants indicated that VBT was delivered after chemotherapy, while 45% of the respondents reported delivering the VBT before or between the chemotherapy cycles.

Post-treatment recommendations

Majority of the respondents provided some recommendation to prevent vaginal fibrosis and shortening after VBT alone or VBT combined with external RT. The recommended steps were use of vaginal dilatators (78%) or resuming sexual intercourse at 6 weeks after treatment completion (44%). Most of the respondents (68%) did not recommend a treatment for vaginal dryness, although the use of a vaginal estrogen cream once per week was recommended by 32% of the respondents (Table 3).

Discussion

Randomized studies and guidelines regarding VBT have usually emphasized patients' selection and description of the treatment groups, and have defined VBT as a simple technique that is well tolerated and has minimal side effects [12]. Although published surveys of radiation oncologists have shown variability in the fractionation and planning parameters, most strategies have been aligned with the ABS recommendations [7, 8]. However, there are no clear data regarding VBT strategies in Turkey, which motivated us to survey the TROD gynecological oncology sub-group regarding their current practices for using VBT to treat EC. Furthermore, we evaluated physicians' preferences regarding optional parameters that were not included in the recent American Brachytherapy Task Group Reports [13-19], such as rectum and bladder filling, and measures to prevent vaginal dysfunction. The distribution of responses indicated that CT-based planning was generally performed for the first fraction, a VBT scheme of 5 Gy × 3 fraction was usually applied after external RT (at a dose of 45 Gy), the VBT was generally performed every 2 days, and the dose was prescribed to 0.5 cm from the vaginal mucosa. Common strategies for managing vaginal dryness, fibrosis, and shortening included weekly dilatator use, sexual intercourse, and weekly estrogen cream application.

Patient's anatomy and filling of the rectum and bladder have significant effects on the dose distribution, based on results from both dosimetric and prospective studies [15, 18-22]. Hung *et al*. performed CT-based dosimetric analyses of patients with an empty bladder and after bladder filling with 180 ml of sterile water, which revealed that the distended bladder was associated with lower doses to the small bowel around the vaginal cuff, without significant changes in the doses to the bladder, rectum, or sigmoid colon [15]. Stewart *et al*. compared three bladder filling strategies for each VBT fraction and reported that an empty bladder was associated with lower bladder doses during vaginal cuff HDR brachytherapy [21]. Conflicting results were also observed in Turkish practice, as approximately one-half of the respondents preferred an empty bladder and the remaining ones preferred some degree of bladder filling.

The ABS survey published in 2004 showed that almost all respondents used radiographs for imaging and

VBT planning for each session [7]. However, when similar questions were repeated in the 2014 survey, three-dimensional CT-based planning was preferred by 83.2% of the respondents, although 73.4% of them only used CT planning for the first fraction [8]. Martell *et al*. [10] subsequently surveyed ABS members in 2019 and reported that only 64% of respondents used CT for VBT planning, and only 33% of the respondents repeated the CT planning before each subsequent fraction. Our survey revealed that 65% of Turkish respondents used CT-based planning for the first fraction and 21% repeated the planning for every fraction, which is consistent with the reported use patterns among ABS members.

The ABS surveys have also showed diversity in the dose schedules and dose specifications regarding vaginal length and depth [7-11]. The 2003 ABS survey revealed that almost one-half of physicians used 15 Gy delivered in 3 fractions prescribed to 0.5 cm from the mucosa in patients treated using pelvic RT and VBT, and that the prescribed dose was increased to 21 Gy delivered in 3 fractions when VBT was used alone [7]. The 2014 survey also indicated that approximately one-half of respondents used the same schedule that was defined in the 2004 survey [10]. However, a 2009 survey of the Gynecologic Cancer Intergroup regarding external RT and VBT for EC revealed that there was no agreement regarding the brachytherapy dose, fractionation, or schedule [23]. In addition, although the ABS guidelines aimed to promote consistency between centers, there was only approximately 50% agreement regarding the dose scheme and vaginal length for the dose specification. Our results indicated that one-half of the Turkish radiation oncologists preferred 15 Gy in 3 fractions when the VBT was combined with external RT (45 Gy), although when VBT was used alone, the most common schemes were 21 Gy in 3 fractions, 27.5 Gy in 5 fractions, and 30 Gy in 5 fractions. Long-term results of the PORTEC–2 trial suggest that 21 Gy in 3 fractions is the standard of care, and the ongoing PORTEC-4 study will evaluate the effects of a schedule using 15 Gy in 3 fractions [24]; although that study was revised in 2016 and the first results will not be available until 2028. Nevertheless, the PORTEC-2 strategy (21 Gy in 3 fractions over 2 weeks; three fraction given within two weeks, not in one) has been prospectively validated as an effective local treatment with a low-rate of late vaginal toxicity (3%) [25].

Long-term vaginal toxicities can include vaginal discharge, dryness, itching, bleeding, fibrosis, telangiectasias, stenosis, shortening or narrowing of the vagina, and dyspareunia [26]. The VBT factors that influence vaginal toxicity are dose-rate, fractionation, and length and depth of the treated vagina [13]. Local treatments after VBT can help improve vaginal tropism, elasticity, and lubrication [27]. Park *et al*. [28] evaluated intravaginal HDR brachytherapy for EC and reported that vaginal stenosis was not observed in 67% of patients, although they reported grade 1 stenosis in 26% of patients, grade 2 stenosis in 6% of patients, and grade 3 stenosis in 1% of patients. The risk of grade ≥ 1 stenosis was independently related to the proportion of vagina receiving > 60% of the prescribed dose and a total dose of > 14 Gy, while grade ≥ 2 stenosis was independently predicted by non-use of a vaginal dilator. Law *et al*. also reported that using a vaginal dilatator was effective for minimizing the risk of vaginal stenosis [29]. However, in contrast with the results from that prospective trial, a Cochrane review and another report provided conflicting evidence regarding the routine use of dilatators [29, 30]. A small number of studies have evaluated topical therapies and described improved outcomes after the use of vaginal estrogen applications for acute and late toxicities, especially in terms of dyspareunia, alterations in the vaginal epithelium, and vaginal stenosis [31]. Our study showed that almost 70% of the respondents recommended using a dilator at least once per week as well as estrogen creams based on specific vaginal symptoms. However, there are no widely accepted guidelines in Turkey and other countries regarding the recommended frequencies of dilatator or estrogen cream use. Therefore, studies are needed to clarify the optimal frequency and duration of their use as well as methods for improving adherence.

The present study has several limitations. First, the survey only received 57 responses, which corresponded to only 10% of all Turkish radiation oncologists. Nevertheless, it is important to note that we specifically targeted radiologists that specialize in treating gynecological cancers, which may strengthen our findings regarding routine practice in Turkey. Second, the questionnaire has not been validated in any other study. Third, the questions only addressed the VBT parameters, and did not consider the specific indications or details regarding external RT use. Therefore, a more detailed survey and the development of guidelines may help guide routine practice for managing early-stage and late-stage endometrial cancer.

Although several guidelines have been developed to standardize VBT treatment, there is substantial variability in the routinely used VBT parameters for both endometrioid and non-endometroid cancers [32]. Furthermore, different surveys have also indicated significant variability in treatment's recommendations as well as simulation and planning processes, when using VBT as adjuvant treatment for EC [7-11]. Our survey of the TROD gynecological oncology sub-group also showed similar variability in Turkey, which may be related to differences in institutional experience, infrastructure, and physicians' preference. This survey provides a starting point for better understanding Turkish practices, and we hope to perform additional studies to develop standardized national guidelines, which might be supported by a prospective multicenter study.

Disclosure

The authors report no conflict of interest.

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Appendix

A survey of the Turkish Radiation Oncology Group regarding vaginal brachytherapy application

1. **What dose fraction scheme do you prefer for high-dose-rate vaginal cuff brachytherapy alone?**
   a. 6 Gy × 5 fractions
   b. 4 Gy × 6 fractions
   c. 7 Gy × 4 fractions
   d. 7 Gy × 3 fractions
   e. 5 Gy × 5 fractions
   f. Other

2. **What is the dose fractionation scheme you use for vaginal cuff brachytherapy with external radiotherapy (dose, 45 Gy)?**
   a. 5 Gy × 4 fractions
   b. 7 Gy × 3 fractions
   c. 6 Gy × 3 fractions
   d. 5 Gy × 3 fractions
   e. 6 Gy × 2 fractions
   f. Other

3. **What is the dose fractionation scheme you use for vaginal cuff brachytherapy with external radiotherapy (dose, 50.4 Gy)?**
   a. 4 Gy × 4 fractions
   b. 6 Gy × 3 fractions
   c. 5 Gy × 3 fractions
   d. 4 Gy × 3 fractions
   e. 6 Gy × 2 fractions
   f. Other

4. **What is the frequency of brachytherapy application?**
   a. Every other day (3 days per week)
   b. Every day
   c. Once every three days
   d. Twice per week
   e. Other

5. **Where do you define the dose prescription point?**
   a. Surface
   b. Depth of 0.5 cm
   c. Other

6. **Do you use a urinary catheter during the procedure?**
   a. Yes, at every fraction
   b. Yes, only at the first fraction
   c. No

7. **Do you fill the bladder during vaginal brachytherapy delivery?**
   a. No
   b. Yes, specific volume for each patient
   c. Yes, 10 cc
   d. Yes, 50 cc
   e. Yes, 100 cc
   f. Yes, 150 cc
   g. Other

8. **Do you recommend any bowel preparation?**
   a. Yes, at every fraction
   b. Yes, only at the first fraction
   c. No

9. **Do you use computed tomography-based planning?**
   a. Yes, at every fraction
   b. Yes, only at the first fraction
   c. No

10. **How do you define the length of the vaginal target for dose prescription (endometrial histology)?**
    a. First 3 cm
    b. First 4 cm
    c. Throughout the length of the cylinder
    d. Other (please define)

11. **How do you define the length of the vaginal target for dose prescription (non-endometrial histology)?**
    a. First 3 cm
    b. First 4 cm
    c. Throughout the length of the cylinder
    d. Other (please define)

12. **Do you use vaginal brachytherapy for serous or clear cell histology?**
    a. Yes
    b. No

13. **Are the indications and fraction schedules the same as that for endometrial cancers?**
    a. Yes
    b. No

14. **What is the timing of vaginal brachytherapy for patients who are receiving chemotherapy?**
    a. Before the start of chemotherapy
    b. Between chemotherapy cycles
    c. After the last chemotherapy cycle

15. **When do you recommend resuming sexual intercourse after treatment?**
    a. Any time
    b. One week after the end of treatment
    c. Three weeks after the end of treatment
    d. Six weeks after the end of treatment
    e. Other

16. **Do you provide recommendations regarding the use of dilators and/ or sexual intercourse after treatment?**
    a. Sexual intercourse or dilator use once per week
    b. No

17. **Do you recommend estrogen-based cream for treating vaginal dryness?**
    a. No
    b. Yes, applied once per week