



Adjuvant Radiotherapy Approach in Stage I High Risk and High-intermediate Risk Endometrioid-type Uterine Cancers TROD 04-005 Gynecological Tumors Subgroup Survey Study

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OBJECTIVE

Evaluation of adjuvant therapy approach in Stage I, high and high-intermediate risk endometrioid-type uterine cancers with a survey.

METHODS

Our survey, which was designed as the Turkish Society of Radiation Oncology-Gynecological Tumors Subgroup Study asked adjuvant therapy preference (ATP) according to different scenarios.

RESULTS

A total of 122 people participated in the survey. Myometrial invasion and grade were chosen the most frequently evaluated prognostic factor. In patients with Stage 1A-B, Grade 1-2, lymphovascular invasion (LVI) (+) as determined by the staging surgery (SS), the ATP was 68% for vaginal brachytherapy (VB). In 48 (40%) participants who did not recommend SS for the patient without SS, the recommendations were external radiotherapy (ERT)+VB in 33%. In Stage 1A, Grade 3, LVI (-) patients who had undergone SS, the ATP was 63% for VB. For LVI (+) patients in the same group, the ATP was 43% for ERT+VB. In 39 (32.5%) participants who did not recommend SS for the patient without SS, the recommendations were ERT+VB in 43%. In Stage 1B, Grade 3, LVI (-) patients who had undergone SS, ATP was 45% for ERT+VB. For the LVI (+) positive patients, the ATP was 71% for ERT+VB. In 31 (26%) participants who did not recommend SS, for the patient without SS, the recommendations were ERT+VB in 55%.

CONCLUSION

Our survey showed that ATP of participants was similar to current guidelines. They preferred adjuvant therapy as a multi-modality treatment instead of single-modality in the presence of prognostic factors, such as not performing SS or LVI.

Keywords: Adjuvant radiotherapy; endometrial cancer; high risk; high-intermediate risk; survey.

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Introduction

Endometrial cancer accounts for 3.6% of all cancers. According to SEER data, 65,620 newly diagnosed pa-

tients are expected in 2020. Its 5-year survival is 81.2%, and it is responsible for 2.1% of cancer-related deaths. [1] The most common subtype is endometrioid-type adeno carcinoma[2] and 80% of these cancers are de-

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tected at an early stage. The 5-year survival rate of these patients is over 95%. [3] The most important prognostic factors affecting the course of the disease are stage, histological grade, histological cell type, degree of myometrial invasion, lymphovascular invasion (LVI), age, and lower uterine segment involvement. [4]

Surgery is the primary treatment for endometrial cancer. Total abdominal hysterectomy + bilateral salpingo-oophorectomy ± pelvic para-aortic lymph node dissection is recommended. After surgery, patients are classified according to risk groups and adjuvant treatment is planned.

The ESMO-ESGO-ESTRO consensus report classifies the FIGO Stage IA, G3 or IA-B, G1-2, and LVI (+) patients diagnosed with endometrioid adenocarcinoma as high-intermediate risk group (HIRG) and the FIGO Stage IB, Grade 3, Stage II-III R0 resection patients with non-endometrioid histology (serous papillary/clear cell) as high-risk group (HRG). [5]

There is no clear consensus about the adjuvant therapy decisions for patients diagnosed with HIRG and HRG endometrial cancer. Different treatment options are available in various guidelines and clinical protocols. In this study, our aim was to examine the factors that affect the treatment decisions by physicians working in radiation oncology for patients with HIRG and HRG EC and to present the choice of adjuvant therapy for this group of patients.

Materials and Methods

Type, Population, Sample, Place, and Date of the Study

Our study was designed as a survey in the TROD Gynecological Tumors Subgroup. The study population is composed radiation oncology physicians working in university hospitals, training and research hospitals, state hospitals, and private centers who have received a survey and answered questions voluntarily. The surveys were distributed and answered from July 2019 to October 2019.

Study Variables

The independent variables of the study are questions containing socio-demographic data, and the dependent variables are the scenarios provided according to the risk classification.

Data Collection Method and Tools

In the study, the participants were asked 19 questions, six of which were about socio-demographic data. Apart

from the socio-demographic data questions, the first two questions were about the guidelines/protocols used in making treatment decisions. The second one was about the prognostic factors that determine the adjuvant therapy decision in endometrial cancer in the literature. Questions 9-19 asked which adjuvant therapy option(s) would be preferred by the participants in scenarios with HIRG and HRG patients created according to the risk groups defined in the ESMO-ESGO-ESTRO 2016 guidelines. For each scenario example, the following choices were presented: (a) Observation, (b) vaginal brachytherapy (VB), (c) external radiotherapy (ERT), (d) ERT+VB, and (e) Other. Again, for each scenario, the participants were asked whether they would recommend staging surgery (SS) before an adjuvant therapy decision if SS had not been performed. Table 1 presents the survey questions. In addition, we also asked about participant preferences according to whether SS was performed or not when making a treatment decision.

Statistical Analysis

Statistical analyzes were performed using SPSS version 17.0 software. The compliance of the variables to normal distribution was examined using analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). Descriptive analyzes were presented using mean ± standard deviation for normally distributed variables. Descriptive statistics were made by giving frequency and percentage values in categorical data. In continuous data, a t-test was used in independent groups in normal distribution to compare two groups. One-Way ANOVA analysis was used to compare more than two groups. Bonferroni analysis was used for *post hoc* analysis. Pearson's Chi-square or Fisher's Exact Chi-square test was used in the analysis of categorical data. Cases where the P-value was below 0.05 were considered statistically significant.

Results

A total of 122 people participated in the survey. The survey completion rate was 98%. The median age was 41 years (25-59 years). Median work experience was 12 (1-39) years, and the median annual average number of patients with endometrial cancer seen by the participants was 25 (1-500). Information obtained from socio-demographic questions is shown in Table 2.

101 (84%) of the participants were using NCCN, 33 (27.5%) ASTRO, 23 (19%) ESGO guidelines, and 30 (25%) their own clinical protocols for ATP. In this question, participants were allowed to select more than one choice.

Table 1 Survey questions

Question 1: Age:	
Question 2: Gender	
(a) Female (b) Male	
Question 3: Institution of employment	
(a) State hospital (b) Research and training hospital (c) University (d) Private (e) Other	
Question 4: How many years of experience do you have in radiation oncology?	
Question 5: Are you an academic staff member at your institution?	
(a) Yes (b) No	
Question 6: How many patients diagnosed with endometrial cancer do you see annually on average?	
Question 7: Which guideline's recommendations do you prefer to evaluate in the treatment decision? (More than one choice can be selected)	
(a) NCCN (b) ESGO (c) ASTRO (d) My own clinic's treatment protocol (e) Other	
Question 8: Which prognostic factor is most important when making the decision for adjuvant therapy in endometrioid-type uterine cancer? (More than one can be selected)	
(a) Age (b) Grade (c) LVI (d) Tumor size (e) myometrial invasion depth (f) Lower uterine segment involvement (g) endocervical glandular involvement (h) Other	
Question 9: What is your preference for adjuvant therapy in Stage 1 A-B, Grade 1-2, LVI (+) patients who have undergone SS?	
(a) Observation (b) VB (c) ERT (d) ERT+VB (e) Other	
Question 10: Would you recommend SS before an adjuvant treatment decision in Stage I A-B, Grade 1-2, LVI (+) patients who have not undergone SS?	
(a) Yes (b) No	
Question 11: If your answer to the previous question is no, what is your preference for adjuvant therapy in Stage 1 A-B, Grade 1-2, LVI (+) patients who have not undergone SS?	
(a) Observation (b) VB (c) ERT (d) ERT+VB (e) Other	
Question 12: What is your preference for adjuvant therapy in Stage 1A, Grade 3, LVI (-) patients who have undergone SS?	
(a) Observation (b) VB (c) ERT (d) ERT+VB (e) Other	
Question 13: What is your preference for adjuvant therapy in Stage 1A, Grade 3, LVI (+) patients who have undergone SS?	
(a) Observation (b) VB (c) ERT (d) ERT+VB (e) Other	
Question 14: Would you recommend SS before an adjuvant treatment decision in the Stage IA, Grade 3 patient group who have not undergone SS?	
(a) Yes (b) No	
Question 15: If your answer to the previous question is no, what is your preference for adjuvant therapy in Stage 1A, Grade 3 patients who have not undergone SS?	
(a) Observation (b) VB (c) ERT (d) ERT+VB (e) Other	
Question 16: What is your preference for adjuvant therapy in Stage 1B, Grade 3, LVI (-) patients who have undergone SS?	
(a) Observation (b) VB (c) ERT (d) ERT+VB (e) Other	
Question 17: What is your preference for adjuvant therapy in Stage 1B, Grade 3, LVI (+) patients who have undergone SS?	
(a) Observation (b) VB (c) ERT (d) ERT+VB (e) Other	
Question 18: Would you recommend staging surgery before an adjuvant therapy decision in the Stage I B, Grade 3 patient group who have not undergone SS?	
(a) Yes (b) No	
Question 19: If your answer to the previous question is no, what is your preference for adjuvant therapy in Stage 1B, Grade 3 patients who have not undergone SS?	
(a) Observation (b) VB (c) ERT (d) ERT+VB (e) Other	

VB: Vaginal brachytherapy; ERT: External beam radiotherapy; SS: Staging surgery; LVI: Lymphovascular invasion. The survey was completed either face-to-face with the participants who filled in the printed responses or by email and an electronic text and messaging application (Watts-Up[®]) with the help of an electronic file prepared on the Survey Monkey[®] portal

Table 2 Socio-demographic data

Participant	n	%
Gender		
Female	72	61
Male	47	39
Institution of employment		
State hospital	39	33
Research and training hospital university	39	33
University	22	18
Private	19	16
Academic staff		
Yes	43	36
No	77	64
Professional experience		
1-10 years	47	39
11-20 years	55	46
21-30 years	16	13
31-40 years	2	2
Annual number of patients		
1-50 patients	94	79
51-100 patients	17	14
>100 patients	7	7

Myometrial invasion was chosen by 112 (93%) and grade by 109 (91%) people as the most frequently evaluated prognostic factors when making treatment decisions. Among the given options, tumor size was chosen as the least evaluated prognostic factor by 36 (30%) participants. In this question, participants were allowed to select more than one choice. In Table 3, the evaluation percentage of prognostic markers given in the survey while performing ATP is given.

In (LVI) (+) (HIRG) patients with Stage 1A-B, Grade 1-2, LVI who had undergone SS, the ATP percentage was 68% for VB, 11% for ERT, 9% for ERT+VB, and 7.5% for observation ($p < 0.0001$ in favor of VB). If SS had not been performed on the same group, 72 (60%) of the participants recommended SS. In 48 (40%) participants who did not recommend SS to this group, the recommendations were ERT+VB in 33%, VB in 26%, ERT in 24%, and observation in 4.5% ($p = 0.001$ in favor of ERT+VB).

In Stage 1A, Grade 3, LVI (-) patients (HIRG) who had undergone SS, the ATP was 63% for VB, 22.5% for ERT+VB, 9% for ERT, and 5% for observation ($p < 0.0001$ in favor of VB). For LVI (+) patients in the same group, the ATP was 43% for ERT+VB, 41% for VB, 14% for ERT, and 1% for observation ($p < 0.0001$ in favor of ERT+VB). 81 (67.5%) participants recommended SS for Stage 1A, Grade 3 patients who had not

Table 3 The ratio of prognostic markers to be evaluated in ATP

Prognostic factor	Participant (n)	%
Myometrial invasion depth	112	93
Grade	109	91
LVI	95	79
Age	64	53
Endocervical glandular involvement	47	39
Lower uterine segment involvement	46	38
Tumor size	30	30

ATP: Adjuvant therapy preference; LVI: Lymphovascular invasion

undergone SS. In 39 (32.5%) participants who did not recommend SS for this group, the recommendations were ERT+VB in 43%, ERT in 24.5%, VB in 20%, and observation in 1.5% ($p < 0.0001$ in favor of ERT+VB).

In Stage 1B, Grade 3, LVI (-) patients (HRG) who had undergone SS, ATP was 45% for ERT+VB, 35% for VB, 19% for ERT, and observation was not recommended ($p < 0.0001$ in favor of ERT+VB). For the LVI (+) patients in the same group, the ATP was 71% for ERT+VB, 14% for ERT, 13% for VB, and 1% for observation ($p < 0.0001$ in favor of ERT+VB). 89 (74%) participants recommended SS to Stage 1B, Grade 3 patients who had not undergone SS. In 31 (26%) participants who did not recommend SS, the recommendations were ERT+VB in 55%, ERT in 20%, and VB in 11% ($p < 0.0001$ in favor of ERT+VB).

Table 4 summarizes data considered statistically significant after evaluating the correlation between questions nine through 19 in which demographic questions, selected guides, and possible scenarios are given. Each of the demographic data and question choices was compared separately, and data with $p < 0.05$ were shared in the table. There was no significant value in statistics regarding years of experience and age. Gender was not taken into consideration. In terms of guidelines, only data of those who preferred NCCN were considered significant in six questions.

Discussion

Surgery is the primary treatment method for endometrial cancer. Post-surgical radiotherapy is an important adjuvant therapy modality preferred as external and/or brachytherapy alone. Although there are a great number of studies, a clear consensus has not been established on the choice of adjuvant therapy. In daily practice, NCCN, ASTRO, and guidelines are used most

Table 4 Relationship between demographic data, selected guidelines, and scenarios

Demographic data	Question 9-19	Option	p
Institution of employment			
Research and training hospital	Question 15	ERT+VB	0.035
Research and training hospital	Question 16	ERT+VB	0.001
Academic staff			
No	Question 11	ERT+VB	0.023
No	Question 15	ERT+VB	0.007
No	Question 17	ERT	0.005
No	Question 19	ERT+VB	0.004
Guidelines			
NCCN	Question 10	Yes	0.037
NCCN	Question 13	ERT+VB	0.024
NCCN	Question 14	Yes	0.019
NCCN	Question 16	ERT+VB	0.023
NCCN	Question 17	ERT	<0.001
NCCN	Question 19	ERT	0.002

ERT: External beam radiotherapy; VB: Vaginal brachytherapy; NCCN: National Comprehensive Cancer Network

frequently, and the risk classification in which stage and prognostic factors are evaluated together in these guidelines has been able to clearly reveal the risk of recurrence and makes the decision of adjuvant therapy easier. However, guidelines make different recommendations, especially for HIRG patients. The ATP of the guidelines changes according to the surgery performed and prognostic factors.

In early-stage endometrial cancer, the location of SS, that is, of lymph node dissection, is controversial.[5] Although the therapeutic effect of lymph node dissection is unclear, it is complementary to the surgical procedure. The surgery performed allows for the final surgical staging of the patients and makes it easier to decide on adjuvant therapy. However, is lymph node dissection really necessary in early-stage endometrial cancer? Especially in the presence of grade 1-2, <50% myometrial invasion, the possibility of these patients to benefit from lymph node dissection is very low, since the possibility of pathological lymph node will be very low.[6] In a randomized controlled study by Panici et al.[7] 514 patients diagnosed with early-stage endometrial cancer, there was no difference in overall survival and disease-free survival between the two groups with and without lymph node dissection. Similarly, in the ASTEC study, 1,408 Stage I endometrial cancer patients were randomized. No difference was found in the group in which lymph node dissection was performed compared to the group with no lymph node dissection.[8] In the ASTEC study, the small number of lymph nodes removed and the lack of para-aortic dissection were criticized.

There are groups that recommend dissection according to the grade of the tumor, apart from the stage. In the study by Trimble et al.,[9] lymph node dissection was recommended for high-grade tumors. The analysis of Kim et al.,[10] in which 16,995 patients were evaluated in nine studies, showed that ten or more lymph nodes removed were of limited benefit in low-risk endometrial cancer but had an overall survival benefit in intermediate- and high-risk endometrial cancer.

The guidelines state that lymph node dissection does not provide a survival advantage in HIRG patients, but it can be performed for surgical staging, and recommend lymph node dissection for HRG patients.[5]

In the SEPAL study, unlike other studies, lymph node dissection was also recommended for HIRG patients, and in the study that included 671 patients, the survival of 407 HIRG and HRG patients who underwent pelvic and para-aortic lymph node dissection was found to be higher ($p=0.0009$).[11]

In our study, in the scenarios where HIRG and HRG were given, the answer to the question “Would you recommend SS if SS had not been performed” (questions 10, 14, and 18), was “I would recommend SS” with 71% for question 10, 67% for question 14, and 89% for question 18, respectively. All the participants who did not recommend SS when responding to these questions selected the ERT+VB choice in a statistically significant manner. The fact that most of the participants recommend SS indicates that staging by dissection is still preferred by physicians or that lymph node dissection is thought to have therapeutic effect. Those who did not

recommend SS preferred ERT+VB to dissection. The preference of combined therapy shows that physicians believe that dual-modality will be more successful in this group of patients.

Age, myometrial invasion, stage, grade, and LVI are among the most important prognostic factors in endometrial cancer.[12] Prognostic factors used in risk classification in ESMO-ESGO-ESTRO guidelines are LVI, stage, and grade.[5] The GOG-99, ASTEC/EN5, and PORTEC-1 studies determined the risk groups of the study using similar prognostic factors.[13-15] In our study, the participants chose the prognostic markers evaluated during ATP as myometrial invasion with 93%, grade with 90.83%, and LVI with 79.16%, respectively. Although there are studies considering tumor size above 2 cm as a risk factor,[16] tumor size is not among the risk factors in the decision of adjuvant therapy in current guidelines.[5,17] In our study, tumor size was the least evaluated prognostic factor with 30%.

As a result of three extensive, randomized studies comparing ERT and observation in early-stage endometrial cancer, a statistically significant decrease in locoregional recurrence rates was observed in the arm receiving ERT, without observing the overall survival difference.[13-15]

In the PORTEC study, 714 Stage 1B, Grade 2-3, and Stage 1C, Grade 1-2 patients (HIRG) were evaluated according to FIGO 1988. The 10-year locoregional recurrence rate without any difference in survival was found to be 5% and 14% in the RT group and the observation group, respectively ($p < 0.0001$). In the subgroup analysis, the 5-year local recurrence rate in the low-risk group with superficial invasion was the same as the observation group (5%). It was determined that Grade 3 patients in the HRG who had deep invasion were the group that benefited from ERT.[15]

In the GOG-99 study, 392 Stage IB-C and IIA patients were evaluated, and in this study in which LVI was included in the risk classification, the 2-year local recurrence rate in the observation group against RT in HIRG was found to be 6% and 27%, respectively, while a 58% reduction was observed in 2-year vaginal and pelvic recurrence.[13]

In the ASTEC/EN5 study, 905 early-stage patients were evaluated. However, in this study, non-endometrioid-type patients were also included in the group, and RT and VB were applied to both groups (53%). The 5-year cumulative recurrence was 6.1% in the observation group and 3.2% in the RT group, and it was emphasized that the low recurrence in the ob-

ervation group was caused by VB given to 53% of the patients in this group.[14]

Considering the success of VB in local control, the PORTEC-2 study was designed, and 427 patients with HIR factors of FIGO 1988 Stage IB, Grade 3; Stage IC, Grade 1, 2; and Stage IIA, Grade 1, 2 (all Stage I patients according to FIGO 2009 staging) were randomized to ERT and VB arms. There was no statistically significant difference in overall survival and local control, but VB was superior in side effects and function evaluation. In the 10-year analysis, pelvic recurrence was slightly higher in the VB arm, though not statistically significant, with 2.5% versus 0.5%, but most of these recurrences were associated with distant metastasis. It was reported that ERT provided better pelvic control in patients with LVI compared to VB.[18]

In Sorbe's et al.[19] study, VB and ERT+VB groups were compared in HIRG. It was emphasized that combined therapy should be used in the HRG. BRT is considered the international standard treatment in HIRG, taking into account the side effects and quality of life data.[20]

In guidelines, the first choice of NCCN in HIRG is VB, and it is recommended to consider it for ERT, especially in the presence of LVI, by looking at other risk factors.[17] The ESGO guidelines determine whether SS is performed in the presence of Stage IA-B, Grade 1-2, LVI, and recommend BRT if SS is performed, and ERT if it is not. In Stage IA, Grade 3, VB is recommended regardless of LVI. In HRG, on the other hand, ERT appears as the first option.[21]

In our study, in accordance with the literature, the recommendation for patients who had undergone SS in questions 9-12, which asked about adjuvant treatment preference in HIRG, was 68% and 63% VB, respectively. In question 13, in the presence of two important prognostic factors of Grade 3 and LVI, combined treatment (ERT+BRT) was preferred at 43%, similar to the Norwegian study.[22]

In our study, in HRG which had undergone SS, the response to questions 16 and 17 was ERT+VB at 45% and 71%, respectively. Participants preferred combined therapy in the presence of two main risk factors, as in HIRG, although ERT was recommended in the guidelines. In patients without SS, combined ERT+VB was the most preferred option regardless of LVI. As 16% of the participants who answered no in this question preferred the "Other" option, we understand that they considered a treatment option combined with possible chemotherapy.

Factors such as the guidelines chosen in treatment decisions, the experience of the physician, whether he/she works as academic staff, and the technical facilities of the institution he/she works for gain importance. In our study, when we compared these data and treatment preferences, no significant correlation was found between physician age and duration of experience and treatment preferences ($p>0.05$). However, in the case that non-academic staff members did not recommend SS in any scenario, their treatment preference was ERT+VB in a statistically significant manner (for questions 11, 15 and 19, $p=0.023$, $p=0.007$, and $p=0.004$, respectively). Combined therapies were considered as a safer and preferable option, especially by non-academic physicians. Similarly, it was observed that those who used the NCCN guidelines recommended SS in a statistically significant manner in questions 10 and 14 ($p=0.037$ and 0.019 for questions 10 and 14, respectively).

The inadequacies of the study were the lack of elaboration about systemic therapy due to questioning the choice of adjuvant RT, and failure to discuss genetic markers as they had not yet been put into daily practice.

Although the preferences of Turkish Radiation Oncology physicians in the choice of adjuvant therapy in early-stage endometrial cancer were different from each other, they were compatible with current guidelines. However, the preference of ERT+VB was observed to increase with the increase in risk factors, unlike the guidelines. Especially in Grade 3 disease without SS, the preference of ERT+VB was observed to be prominent among physicians not working in university and training hospitals. The fact that these choices are not dependent on demographics is proof that the treatments in our discipline are planned in the light of evidence-based data. The evaluation of our results in line with our treatment decisions in a national database, and the creation of our own data and treatment algorithm, should be among our most important goals.

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