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Original Article

Clinicopathologic characteristics of recurrent endometrioid endometrial cancer patients and analysis of methods used during surveillance☆

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ABSTRACT

Objective: To determine cilinicopathologic characteristics of recurrent endometrioid type endometrial cancer patients and analyze the methods applied in detection of recurrent disease during follow-up period.
Methods: We have retrospectively reviewed the file records of the 226 patients who had endometrioid type carcinoma. Bimanual pelvic examination, speculum examination, carcinogenic antigen-125 (CA125) testing, vaginal cuff cytologic screening, transabdominal ultrasound (TAUS) and transvaginal ultrasound (TVUS) imagings were performed within the context of routine follow-up control examinations in the post-treatment period in every 3 months within the first 2 years and in every 6 months in the following 2 years and with annual control in the consecutive years.
Results: Mean follow-up durations was 25.7 ± 18.9 months while recurrence rate was 3.1%. The study patient group underwent totally 1116 times TVUS and 1084 times whole TA-US evaluations, 973 times vaginal cuff cytological screening, 1125 times pelvic and general physical examinations beside 1060 times CA-125 testings were performed in accordance with our routinely performed follow-up protocol. The asymptomatic recurrent cases ; one of those was dignosed with pelvic examination while diagnosis was established using TA-USG evaluation in the other asymptomatic patient. The other 5 cases were symptomatic. Pelvic examination, Computed Tomograhy and Magnetic Resonance Imaging were utilized in diagnosing 1, 3 and 1 of those patients, respectively.
Conclusion: The presence of symptoms and pelvic examination seem to be the most effective modalities in detecting recurrence in follow-up of endometrial cancer. It would be reasonable to optimize intervals between follow-up visits and to determine the appropriate evaluations by considering risk levels of the patients.

INTRODUCTION

Endometrial cancer is the most common gynecological cancer type with a progressively increasing incidence (1). Even though, the reasons of increased incidence is not yet clear, this elevation may be partially explained by several clinical phenomena which may be mentioned between the risk factors of endometrial cancer and such as obesity, diabetes mellitus with progressively increasing frequency worldwide. Since primary sign of endometrial cancer is usually abnormal uterine bleeding and subsequently many patients rapidly make a doctor's appointment without a delay, approximately 75% of the patients are diagnosed with endometrial cancer when tumor is limited to the uterus. Both early diagnosis and successful surgical treatment accompanied by adjuvant therapy approaches, when needed may contribute to a 5-year survival in approximately 80% of the patients. The expected 5-year survival rates for Stage 1 and Stage 2 disease were reported as 81-91% and 71-78%, respectively (2). The recurrence rate was reported as 13% for all endometrial cancer types whereas this rate was found approximately 3% in the low-risk patient group (3).

Both increased incidence of endometrial cancer and post-treatment high survival rates create an increasing patient population which requires a close follow-up. Although there are

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no studies which analyze the test methods to utilize in follow-up control survey of endometrial cancer survivors ; follow-up protocols recommended by The National Comprehensive Cancer Network (NCCN) and The American College of Obstetricians and Gynecologists (ACOG) are applied. These guidelines recommend performing physical examination once every 3-6 months in the first 2-3 years and once every 6 months or an annual physical examination in the consecutive years as well as CA-125 level measurement if initially elevated and imaging modalities as clinically indicated (4,5). A systematic review analyzed the modalities applied for detection of recurrence in the endometrial cancer patients and reported that 5-33%, 0-4%, 4-13%, 5-21% and 15% of the asymptomatic patients were diagnosed according to pysical examination, vaginal cytological screening, TAUS, abdominal computed tomography (CT) and increased CA-125 levels, respectively (3). Also European Society of Medical Oncology (ESMO) guidelines on endometrial cancer offers physical and gyneacological examinations as an ultimate method in follow-up ; whereas further investigations are adressed in the case of clinical suspicions (6). On the other hand albeit the recommedations of guidelines ; imaging modalities, vaginal cytologic examinations and blood tests are kept going to be performed in clinical practice. Adherence to current guidelines in follow-up of endometrial cancer patients has been investigated in a recent study from France. They declared the nonadherence to guidelines rate as nearly 50 % (7). Various reasons may contribute to this pertinance on conventional protocols. Especially concerns of missing of a recurrent case may be the reason of redundant surveys and examinations.

In this retrospective cohort study we aimed to reveal the performance of physical and pelvic examination, TAUS and TVUS, blood CA-125 level and vaginal cuff cytologic examinations on detection of recurrence of endometrioid type endometrial cancer patients treated in our clinic. Secondary profit of this retrospective study may be the reinforcement of current guideline recommendations.

MATERIALS AND METHOD

Totally 379 patients treated and followed-up with diagnosis of endometrial cancer and between March 2012 and March 2018 in our tertiary gyneoncologic center were retrospectively analyzed and 226 patients with endometrioid type adenocarcinoma were included in the study. Non-endometrioid histologic types excluded ; since great majority of endometrial cancer is endometrioid type and therefore follow-up burden is also built up by these group of patients. The pathology reports of the patients included in the study were analyzed retrospectively and information about stage and grade of carcinoma and number of the resected lymph nodes were obtained. The International Federation of Gynecology and Obstetrics (FIGO) staging system was used in determination of the stage. Risk groups of early term endometrial cancer patients has been specified according to ESMO recommendations. The demographic characteristics, post-treatment imaging and cytological results, CA-125 values, findings of physical examination and file records of the patients were reviewed and determined. Follow-up schedule for the patients (our routinely applied protocol) included in the study involved follow-up control performed once every 3 months in the post-treatment 2 years, once every 6 months in the consecutive 2 years and annual control examinations in the latter years. General physical examination, bimanual pelvic examination, speculum examination, CA-125 testing, vaginal cuff cytological screening tests, TVUS imagings were performed in each follow-up control. Lung radiography, Computed Tomography (CT), Magnetic Resonance Imaging (MRI) and transabdominal whole abdominal Ultrasonography (TAUS) were also performed in some patients when needed. Power analysis has not been done since we aimed to evaluate the datas of our clinic in this retrospective study. The obtained data was statistically analyzed by using SPSS Statistical Software Version 17.0.

RESULTS

Totally 379 cases of endometrial cancer were treated in our center between the mentioned dates and 226 of those cases were endometrioid type adenocarcinoma to be included in this study in accordance with the inclusion criteria. Surgical treatment was performed in 219 of these 226 patients by the unique gynecologic oncologist in our center while 2 patients were operated in an external medical center and subsequently followed-up in our center. Hysterectomy was performed in 5 patients in an external center and diagnosed with cancer, complementary surgeries of these patients were performed in our clinic. Mean age of the patients was 58.1 ±9.3 years (35-85 years). Median postoperative follow-up duration was 24 months. Of the patients: 167 (%73.9), 32 (%14.2), 8 (3.5%), 1 (0.4%), 4 (1.8%), 10 (4.4%), 1 (0.4%) and 3 (1.3%) were FIGO Stage 1a, Stage 1b, Stage 2, Stage 3a, Stage 3c1, Stage 3c2, Stage 4a and Stage 4b, respectively. With respect to grade; 108 (47.8%), 98 (43.4%) and 20 (8.8%) patients were Grade 1, Grade 2 and Grade 3, respectively. Totally in 198 patients were performed lymph node dissection whereas lymph node dissection was not performed in 28 patients. Mean number of the dissected lymph nodes was 63 ± 24.9 (min:15-max:164). The socio-demographic and clinical characteristics and risk groups of the patients were shown in Table 1.

Postoperative adjuvant therapy was not performed in 153 of patients and follow-up data of 6 patients who were recommended adjuvant therapy could not be obtained. Remaining patients' adjuvant therapies are designated in Table 2.

In the follow-up period, recurrence was detected in 7 (3.1%) of the 226 patients. Recurrence rate was 5.4% in the patients who received adjuvant therapy whereas it was found 1.3% in the patients who did not need adjuvant therapy. Recurrence was encountered by pelvic examination performed after asymptomatic examination, pelvic examination performed due to complaint of vaginal spotting, TAUS performed after an asymptomatic examination, CT performed due to the complaints of lumbar pain, abdominal distention accompanied with fullness and coughing, whole abdominal MRI performed after inadequate USG after an abdominal pain in 1, 1, 1, 3 and 1 patients, respectively. Patient number 5 was operated initially in external center and pelvic lymph nodes were positive in initial pathology report, so although there were not any clinical suspicion, TAUS examination done and lymphadenopathy revealed. Patient number 7 had a loose abdominal pain ; since the patients' US examination was

Table 1
Clinical characteristics of the patients

Age (years) (Mean ± SD)	58.1 ± 9.3
Follow-up (Months, Mean ± SD)	25.7 ± 18.9
Number of Co-morbidities(n, %)	
Hypertension	61(26%)
Diabetes	18(7.9%)
Hypertension plus Diabetes mellitus	54(23%)
Goiter	7(3%)
Breast cancer	2(0.8%)
Cervical cancer	2(0.8%)
Risk Classification	**Number of patients**
Low risk	162 (71,6 %)
Intermediate risk	31 (13.7 %)
High risk	32 (14.1 %)
Number of the resected LN (Mean ± SD)	63 ± 24.9

Abbreviations: SD: standard deviation; LN: lymph nodes.

Table 2
Adjuvant Therapies

Type of Adjuvant Therapy	Number of patients (n, %)
No Adjuvant Theraphy	153 (67.7%)
Brachytherapy	37 (16.4%)
External Radiotherapy	1 (0.4%)
Brachytherapy + ERT	6 (2.7%)
Chemotherapy	10 (4.4 %)
Chemo + radio + Chemo	9 (4%)
Radiotherapy + Chemo	4 (1.8%)
No Consent	6 (2.7%)
Total	226 (100%)

Abbreviations: ERT: external radiotherapy; Chemo: chemotherapy; Radio: radiotherapy

suboptimal magnetic resonance imaging performed. The detailed characteristics of the recurrent patients were shown in Table 3.

It was determined that totally 1116 TV-USG and 1084 whole TAUS evaluations, 973 vaginal cuff cytological screenings, 1125 pelvic and general physical examinations beside 1060 CA 125 testings were performed during follow-up process of the patients in accordance with our routinely performed follow-up protocol.

Abnormal examination findings were detected in 21 cases and recurrence was determined in 2 cases according to the results of advanced investigations which continued with finding of pelvic examination. Ca-125 levels were over 35 IU in 7 cases however recurrence was diagnosed in none of these patients with high Ca-125 levels.

Of US examinations; 1070 (95.8%) were found normal.Abnormal findings of US examinations are denoted in Table 4. The number of the patients with lymphocele was 26, lymphocele was encountered in 37 US examinations since lymphocele was persistent in some of the patients.

The results of the vaginal cuff cytological screenings revealed that 942 smears (96.8%) were normal ; abnormal cytologic results are shown in Table 5. Colposcopic examination was recommended for all the patients with cytological anomalies however this procedure was performed in only 17 patients due to their consents. Biopsy was not needed since normal colposcopic results were obtained in 15 colposcopic examinations. Vaginal cuff biopsies were reported to be normal in 2 patients (LSIL and ASC-US, respectively)

Table 4
The results of US examination during follow-up

	USG examinations (taus-tvus)(n)	%
Normal	1070	95,9
Lymphocele	37	3
Vaginal mass	4	0.3
Ascites	3	0.2
Pancreatic mass	1	0.08
Total number	1116	100

Table 5
The results of vaginal cuff cytology during follow-up

	Vaginal Cuff Cytology (n)	%
Normal	942	96.7
ASCUS	15	1.5
ASCH	4	0.4
AGC	3	0.3
LSIL	2	0.2
HSIL	2	0.2
Inadequate	5	0.5
Infection	1	0.01
Total	973	100

DISCUSSION

Patients' sympthoms and pelvic examination seem to be the most efficient components of follow-up surveys of endometrial cancer patients. Whereas significant benefit of imaging modalities, blood tests and aginal cytology is not ascertained. From this point of view ; results of this study stands by the current guidelines relevant to this issue.

It was stated that 100,000 newly diagnosed endometrial cancer cases in Europe according to Globocan 2012 data and cumulative incidence of endometrial cancer was reported 1.7% (8). Despite absence of a prospective study which analyze the test methods used in follow-up of the endometrial cancer patients, the follow-up schedules recommended by the guidelines of NCCN and ACOG are usually applied in those patients. These guidelines recommend performing physical examination once every 3-6 months in the first 2 years and once every 6 months or an annual physical examination in the consecutive years as well as CA-125 level measurement if initially elevated and imaging modalities as clinically indicated (5). It has been recommended in the literature that stage 1 grade 1-2 endometrial cancer cases should receive control examination once every 6 months in the first year and annual controls in the consecutive years whereas the cases with high risk for recurrence should receive control examinations once every 3 months in the first post-treatment 1-2 years and once every 6 months after 2 nd to 5th years. (6,9). It is additionally stated that each clinic should establish its own follow-up guideline.

The 226 endometrioid type endometrial cancer patients whose treatment protocols were completed in our clinic were strictly followed-up with a schedule involving control examinations performed once every 3 months in the post-treatment first two years, once every 6 months in the consecutive 3rd and 4th years and annually starting from the 5th year. Namely we have applied routine follow-up protocol recommended for high risk patients by the guidelines in all study patients. During every control examination, each patient was evaluated with physical

Table 3
The characteristics of the patients with recurrence

No of patient	Stage-grade	Time of the Recurrence	Symptom	Adjuvant therapy	Localization Of the Recurrence	Post-recurrence Therapy	Modality
1	1AG2	11th month	-	-	Vaginal cuff	Chemo + RT + Chemo	PE
2	1AG1	10th month	Vaginal bleeding	-	Vaginal cuff	BRT	PE
3	3CG1	6th month	Coughing	-	Diffuse in the lung	Chemo	CT
4	2G2	7th month	Lumbar pain	ERT + BRT	Paraaortic LN	Chemo	CT
5	2G1	8th month	-	BRT	Paraaortic LN	Chemo + RT + Chemo	TA USG
6	3CG2	7th month	Abdominal distention	ERT + BRT	Liver, right ureter	Chemo	CT
7	1AG1	12th month	Abdominal pain	BRT	Pancreas	Chemo	MRI

Abbreviations: Chemo: chemotherapy; RT: radiotherapy; Radio: radiotherapy; ERT: external radiotherapy BRT: Brachytherapy; PE: pelvic examination; CT: Computed Tomography; MRI: Magnetic Resonance Imaging (MRI)

examination, TVUS, TAUS, CA-125 testing, vaginal cytological screening test and abdominal examination.

The detection rate of recurrence by physical examination, vaginal cytological screening, increased CA-125 level and CT were reported to be 35-68%, 0-7%, 15% and 0-20% in the literature, respectively (9). Some studies have reported that symptoms and pelvic examination have a detection strength of approximately 80% for recurrence (10). Twenty-one abnormal pelvic examination results were encountered in our study. An ulcerated lesion was encountered in the vaginal cuff of 2 recurrent cases by pelvic examination and these were reported to be recurrent tumors according to the result of biopsies. One of these patients had also complaints of vaginal bleeding and vaginal leucorrhoea. During study peiod, 1125 pelvic examinations were performed while anomalies and recurrences were found in 1.86% and 0.17% of those pelvic examinations, respectively. Also 9.5% of the cases with abnormal pelvic examination results had recurrence. It may be suggested from this aspect that standardization of abnormal pelvic examination and consequently evaluating only the cases with abnormal pelvic examination results by the gynecologic oncologist would be more reasonable.

During follow-up process, totally 1116 TVUS imagings were performed and 95% of those resulted normal. From the recurrent cases, TVUS also revealed masses in 2 patients with vaginal cuff mass encountered by pelvic examination. Recurrence was detected solely by result of TVUS in none of the patients. This outcome of our study is compatible with the studies in the literature which have stated that role of routine US in detection of endometrial cancer recurrence is limited (11,12). However, it may be considered that its use in the cases with abnormal results according to routine pelvic examination may be helpful.

CA-125 level measurement were performed 1060 times in our study and were found 35 IU and above for 7 times. Increased levels of CA-125 were detected in none of the recurrences while no case had an increased level of CA-125 also during the follow-up process. Some studies in the literature have stated that CA-125 levels were high in approximately 60 % of the recurrent cases and that it may increase also due to the effect of radiotherapy (13,14). A study has reported that CA-125 levels play no role in follow-up of especially in early stage endometrial cancer patients (9). Our study revealed compatible outcomes with the literature data since 88 % and 71 % of our study patients were Stage 1 and carrying low risk, respectively.

It would be reasonable to involve vaginal cuff cytological screening in the test content of follow-up controls since most of the recurrences occur in the vaginal cuff. On the other side, detection strength of cytological screening in detection of recurrence ranges between 0-7% (9). However, none of the recurrences was encountered by cytological screening in our study. It has been stated in some studies that detection rate and diagnostic utility of vaginal cytological screening in detection of recurrence is very low and limited as well as being seriously high-cost in routine practice (12,15). From this point of view, the results are compatible with the literature. On the other hand, recurrence detection rate of vaginal cytological screening may vary in the patient groups with high risk for recurrence.

Doubtlessly the essential objective of the follow-ups after primary treatment is the early detection and treatment of the potential recurrence while monitoring efficacy and side effects of the performed treatment and also relieving anxiety originating from cancer. ENDCAT study, which was conducted on the early-term endometrial cancer patients, has compared the efficacy of hospital-based and phone call-based follow-ups with respect to psychological comorbidities and patient satisfaction and concluded an outcome that phone call-based follow-up does not cause psychological and physical injury. (16). Besides, another study published in U.K. has analyzed the tests used by the healthcare professionals in follow-up processes after primary treatment of gynecological cancers on a survey-based design and concluded that there is wide variety on this subject and that phone call-based or nurse-based follow-up strategies are preferred less than conventional follow-up protocols (17).

In our study, 71 % of the recurrent cases were symptomatic therefore presence of symptoms appear as the strongest modality in prediction of recurrence. Beside this presence of recurrences encountered in the some asymptomatic cases and regarding the fact that sympthoms may be absent in the early terms make us consider that questioning presence of symptoms may be insufficient for detection of recurrence. On the other side, absence of a specific symptom is another handicap. Suggesting a follow-up protocol based on completely presence of symptoms indenpendent from testings requires courage and number of our patients has a limited detection strength to suggest this system. The application of a follow-up protocol based on investigating every kind of symptom accompanied by pelvic and physical examinations in low risk patients with low recurrence rates may be a reasonable construction. Although the number of recurrent case in this cohort is limited ; this is the expected case for this population since majority of patients are in low risk group. Indeed studies with extended number of patients may have additional benefit.

As a conclusion ; patient's sympthoms together with physical examination including pelvic bimanuel and speculum examinations have the greatest profit both in terms of cost and efficiency in follow-up surveillance of endometrial cancer patients. Routine imaging and blood surveys seem inefficient according to our findings. Vaginal cuff cytologic examination also had not any additional benefit in this cohort in terms of recurrence detection. These results are consistent with current guidelines which are recommending the sympthoms as a mainstay of surveillance. Although this is not a cost-effectiveness study ; conventional and defensive approaches may have some detrimental effects in terms of cost and time. At least for low risk group extensive investigations should be reserved for patients with high suspicion of recurrence ; beside, patients' every sympthoms should be taken into account during follow up and this must be the mainstay of surveillance for this group of patients.

Compliance with ethical standards

There is no conflict interest between the authors.

This study had been approved by Baskent University Medical School Ethical Comittee with the project number KA18/231.

CRediT authorship contribution statement

S.Y. Simsek: Conceptualization, Software, Formal analysis, Investigation, Data curation, Writing - original draft. **G. Serbetcioglu:** Software. **S. Alemdaroglu:** Software, Data curation, Investigation. **S. Yetkinel:** Software, Data curation. **G.D. Durdag:** Data curation. **H. Celik:** Methodology, Validation, Formal analysis, Investigation, Writing - original draft, Supervision, Project administration.

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