

Use of preoperative and intraoperative parameters for decision making in ovarian preservation in endometrial adenocarcinoma

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Objective: To investigate the characteristics of endometrial adenocarcinoma (EC) patients with ovarian metastasis and to define criteria for ovarian preservation by using preoperative and intraoperative parameters. **Methods:** Clinical and pathological characteristics of patients with EC were reviewed. Following univariate and multivariate analysis to determine factors associated with ovarian metastasis, different sets of criteria were analyzed to determine the subgroup of patients with negligible risk of ovarian metastasis. **Results:** 725 patients were included. Ovarian involvement was detected in 9.1% of patients. Univariate analysis showed that tumor diameter, grade, histological type, myometrial invasion, peritoneal cytology, lymphovascular space invasion (LVSI), cervical invasion, omental and lymph node metastasis are significantly associated with ovarian metastasis while only LVSI, cervical invasion, omental and lymph node involvement were significant on multivariate analysis. By using preoperative and intraoperative parameters only, no ovarian involvement was seen in patients with endometrioid tumor of any grade without myometrial invasion, patients with grade 1, less than 2 cm endometrioid tumors without deep myometrial invasion and in patients younger than 45 years with grade 1 or 2 endometrioid tumors without deep myometrial invasion. **Conclusion:** Ovarian involvement in cases of endometrial carcinoma occurs in less than 10% of cases. Ovarian preservation could be considered in cases of endometrioid adenocarcinoma that meet certain preoperative and intraoperative criteria.

Keywords

Endometrial adenocarcinoma; Ovarian metastasis; Oophorectomy; Ovarian preservation

1. Introduction

Endometrial cancer is the most common malignancy of female genital tract in developed countries and also in Turkey [1, 2]. Endometrioid type adenocarcinoma, which is associated with long-term unopposed estrogenic stimulation accounts for 75–80% of cases and is staged surgically according to the FIGO (International Federation of Gynecology and Obstetrics) revised staging system [3, 4]. The recommended standard surgery includes total hysterectomy and bilateral salpingo-oophorectomy with lymphadenectomy when necessary. Due to up to 5% risk of ovarian metastases in clini-

cally stage I disease, bilateral oophorectomy is recommended for all patients irrespective of age even when the ovaries look normal. Also, the risk of synchronous endometrium-ovarian cancer is around 5–15%, especially in young patients. Furthermore, ongoing estrogen production from the preserved ovaries may activate microscopic residual disease foci which may be associated with increased recurrence rate since endometrial cancer is an estrogen-responsive tumor [5–7].

On the other hand, although endometrial adenocarcinoma is mainly considered a disease of postmenopausal women, 10–15% of patients are diagnosed at premenopausal period and bilateral oophorectomy results in surgical menopause associated with short and long-term sequelae, including vasomotor symptoms and metabolic syndrome [8–11]. This is especially important for young patients in whom favorable prognosis with longer survival is more common [12]. Quality of life related to oophorectomy should be considered in these patients. Thus, the gynecologists face a difficult choice within this context. Although some studies demonstrated that preservation of ovaries in selected patients does not adversely affect oncological outcome, this issue is controversial and further studies are required to reveal patients with endometrial adenocarcinoma without significant risk of ovarian involvement [13–16].

The aim of this study was to examine the clinical and pathological factors associated with ovarian metastases in patients with endometrial adenocarcinoma and to reveal subgroup of patients in whom ovaries can safely be preserved by using preoperative and intraoperative parameters.

2. Materials and methods

Patients who were operated with a diagnosis of endometrial adenocarcinoma at Hacettepe University Faculty of Medicine, Department of Obstetrics and Gynecology were identified from January 2000 to August 2019. The clinical and pathological features of these patients were retrospectively obtained from the electronic medical record system, from the patients' files and from the weekly tumor board forms. Patient's age, menopausal status, operation informa-

tion such as surgical procedure, size of endometrial tumor, histological type, tumor grade presence and depth of myometrial invasion, lymphovascular space invasion (LVSI), cervical and adnexal involvement, peritoneal cytology positivity, omental and retroperitoneal lymph node metastasis and FIGO stage were analyzed. For patients with endometrial autolytic changes in hysterectomy specimens, the grade and histological type reported on biopsy specimens were taken into consideration.

All surgical procedures were performed by gynecologist oncologists and specimens were assessed by pathologists specialized in gynecological cancers. Before 2010, all patients had undergone through comprehensive surgical staging, consisting of total hysterectomy with bilateral salpingo-oophorectomy, bilateral pelvic-periaortic lymphadenectomy, omentectomy or omental biopsy if their medical condition was favorable. After 2010, the extent of the surgery was finalized according to the risk factors determined during pre-operative and intraoperative evaluations [17–19]. Decisions on whether to perform lymphadenectomy or on what extent to perform lymphadenectomy were made based on the criteria which suggested as indicative of low risk for nodal metastases according to frozen section evaluation (less than 50% myometrial invasion, tumor less than 2 cm, well or moderately differentiated histology). Sentinel lymph node mapping was not used in any of the patients. Comprehensive surgical staging was performed when frozen section was unavailable or uninformative.

Patients previously diagnosed with a gynecological cancer who underwent surgical and/or medical treatments, patients with synchronous ovarian and endometrial cancer, patients who were diagnosed with endometrial adenocarcinoma outside of our center (without confirmation of the diagnosis at our Pathology Department) were excluded. Similarly, patients who underwent vaginal hysterectomy without additional surgery, due to unfavorable health conditions were also excluded, as well as patients with macroscopic ovarian involvement and those with clinical advanced stage disease (FIGO stages III–IV). The differentiation between primary or metastatic cancers of the endometrium and ovary was made by using the pathological criteria defined by Ulbright and Roth [20] and by Scully *et al.* [21]. Accordingly, the pathological features for endometrial tumor with ovarian metastasis include large endometrial tumor with small ovarian tumor, presence of atypical endometrial hyperplasia, deep myometrial invasion, direct extension into the adnexa, vascular space invasion in myometrium, spread elsewhere in typical pattern of endometrial carcinoma, bilateral ovarian tumor, hilar location, vascular space invasion, and surface implants in the ovary without ovarian endometriosis.

The study was approved by the Non-Interventional Clinical Research Ethics Board of Hacettepe University Faculty of Medicine (approval number GO 19/753) as thesis for specialty in Obstetrics and Gynecology. SPSS (Statistical Package for Social Sciences for Windows, Armonk, NY, USA: IBM

Corp.) version 22.0 was used for the recording and analysis of data. Pearson's chi-squared test or Fisher's exact test was used to compare categorical variables and *t*-test or Mann-Whitney U test was used to compare continuous variables. Logistic regression analysis was used to identify risk factors associated with ovarian metastasis. A *p*-value of less than 0.05 was considered to be statistically significant and all statistical tests were two-sided.

3. Results

A total of 725 patients were included in the study. Mean age of the patients were 60.8 ± 10.2 years (range 26–86 years). Of these patients, 76 (10.5%) were premenopausal, 39 (5.4%) were less than 45 years of age and only 14 (1.9%) were less than 40 years of age. The most common histological type was endometrioid type adenocarcinoma which was detected in 565 patients (77.9%). Among the non-endometrioid histologies, serous adenocarcinoma was the leading type followed by carcinosarcoma and clear cell adenocarcinoma (9.2%, 5.9%, and 3.5%, respectively). Tumor was well-differentiated (grade 1) in 377 patients (52.0), moderately differentiated (grade 2) in 138 (19.0%) and poorly differentiated (grade 3) in 210 (29.0%) (Table 1). Non-endometrioid tumor histologies were included among high grade lesions.

Table 1. Basic characteristics of patients.

Characteristic	
Age (year) (mean \pm SD) (range)	60.8 \pm 10.2 (26–86)
<45 years of age (n, %)	39 (5.4)
<40 years of age (n, %)	14 (1.9)
Menopausal status (n, %)	
Premenopausal	76 (10.5)
Postmenopausal	649 (89.5)
Histological type (n, %)	
Endometrioid	565 (77.9)
Non-endometrioid	160 (22.1)
Serous adenocarcinoma	67 (9.2)
Carcinosarcoma	43 (5.9)
Clear cell adenocarcinoma	25 (3.5)
Others	25 (3.5)
Grade (n, %)	
1	377 (52.0)
2	138 (19.0)
3	210 (29.0)

SD, standard deviation.

Comprehensive surgical staging was performed in 570 patients (78.6%). According to exploration findings and final pathology reports, stage 1 disease was detected in 506 patients (69.8%) (Table 2). Mean diameter of primary tumor was 3.9 ± 2.5 cm, but it was less than 2 cm in 15.0% and less than 3 cm in 33.4% of the patients. The tumor was superficial (confined to endometrium) in 13.8%. Among the remaining, 42.1% had

superficial (<50%) and 44.1% had deep (\geq 50%) myometrial invasion. LVSI was mentioned in the pathology reports in 69.9% of patients and it was detected to be present in 23.6% of study population. Peritoneal cytology was evaluated in 89.1% and positive cytology was seen in only 9.0%.

Table 2. Surgical-pathological characteristics.

Characteristic	
Surgeries performed (n, %)	
Comprehensive surgical staging*	570 (78.6)
TAH \pm BSO**	108 (14.9)
Others***	47 (6.5)
Stage of disease (n, %)	
Stage 1A	326 (44.9)
Stage 1B	179 (24.6)
Stage 2	55 (7.5)
Stage 3A	34 (4.6)
Stage 3B	1 (0.1)
Stage 3C1	40 (5.5)
Stage 3C2	34 (4.6)
Stage 4A	2 (0.2)
Stage 4B	54 (7.4)
Primary tumor diameter (cm) (mean \pm SD) (range) 3.9 \pm 2.5 (0.0 [†] –24.0)	
<2 cm	109 (15.0)
<3 cm	242 (33.4)
Location of primary tumor (n, %)	
Confined to endometrium	100 (13.8)
With myometrial invasion	625 (86.2)
Superficial (<50%)	305 (42.1)
Deep (\geq 50%)	320 (44.1)
LVSI	
Reported	507 (69.9)
Absent	336 (46.3)
Present	171 (23.6)
Not reported	218 (30.1)
Peritoneal cytology	
Obtained	646 (89.1)
Negative	581 (80.1)
Positive	65 (9.0)
Not obtained	79 (10.9)

SD, standard deviation; TAH, total abdominal hysterectomy; BSO, bilateral salpingo-oophorectomy; LVSI, lymphovascular space invasion.

*TAH + BSO + Bilateral Pelvic + Paraaortic Lymph Node Dissection + Infracolic Omentectomy.

**TAH + BSO only (without lymph node dissection).

***TAH + BSO + omental biopsy or TAH + BSO + bilateral pelvic lymph node dissection with or without omentectomy.

[†]Microscopic tumor.

Ovarian involvement was detected in only 66 patients (9.1%). Table 3 shows univariate analysis carried out to evaluate the relationship between clinical-pathological factors and ovarian involvement. Primary tumor was significantly larger in patients with metastasis to ovaries and tumors equal to or larger than 3 cm in diameter had significantly higher

risk of ovarian involvement. Also, grade, histological type, myometrial invasion, positive peritoneal cytology, lymphovascular space invasion, cervical invasion, omental metastasis and retroperitoneal lymph node involvement were found to be significantly associated with ovarian metastasis. However, menopausal status or age did not affect ovarian involvement.

Table 3. The relationship between clinical-pathological factors and ovarian metastasis.

Parameter	Ovarian metastasis (n, %)		p
	Present	Absent	
	66 (9.1)	659 (90.9)	
Age (years) (mean)	62.3	60.7	0.24
Menopausal status			
Premenopausal, n (%)	5 (6.6)	71 (93.4)	0.42
Postmenopausal, n (%)	61 (9.4)	588 (90.6)	
Tumor diameter (cm) (mean)	5.9	3.7	<0.001
Tumor diameter (2-cm cut-off)			
<2 cm	5 (4.6)	104 (95.4)	0.08
\geq 2 cm	61 (9.9)	555 (90.1)	
Tumor diameter (3-cm cut-off)			
<3 cm	11 (4.5)	231 (95.5)	0.003
\geq 3 cm	55 (11.4)	428 (88.6)	
Grade			
Grade 1	10 (2.7)	367 (97.3)	<0.001
Grade 2	11 (8.0)	127 (92.0)	
Grade 3	45 (21.5)	165 (78.6)	
Histological type			
Endometrioid	26 (4.6)	539 (95.4)	<0.001
Non-endometrioid	40 (25.0)	120 (75.0)	
Myometrial invasion			
Absent	1 (1.0)	99 (99.0)	<0.001
Superficial (<50%)	13 (4.3)	292 (95.7)	
Deep (\geq 50%)	52 (16.3)	268 (83.8)	
Peritoneal cytology			
Negative	26 (4.5)	555 (95.5)	<0.001
Positive	35 (53.8)	30 (46.2)	
LVSI			
Absent	7 (2.1)	329 (97.9)	<0.001
Present	42 (24.6)	129 (75.4)	
Cervical involvement			
Absent	23 (4.2)	519 (95.8)	<0.001
Present	43 (23.5)	140 (76.5)	
Omental involvement			
Absent	35 (5.6)	593 (94.4)	<0.001
Present	30 (57.7)	22 (42.3)	
Lymph node involvement			
Absent	23 (4.2)	522 (95.8)	<0.001
Present	35 (34.3)	67 (65.7)	

Multivariate logistic regression analysis which was performed by using significant factors on univariate analysis identified that ovarian involvement was associated with LVSI, omental involvement, lymph node involvement, and cervical involvement (Table 4).

Table 4. Multivariate analysis results of the parameters associated with ovarian metastasis.

Parameter	<i>p</i>	OR	95% CI
LVSI	0.002	4.3	1.7–11.0
Omental involvement	0.004	4.0	1.6–10.4
Lymph node involvement	0.02	2.6	1.2–5.7
Cervical involvement	0.008	2.8	1.3–6.1

OR, odds ratio; 95% CI, 95% confidence interval.

In addition, sets of criteria were also tested by using uterine parameters which can be identified by preoperative biopsy and intraoperative frozen section evaluation. There were only 39 patients who were suitable for ovarian preservation according to previous literature [6, 8, 18, 19]. These patients had grade 1–2, endometrioid type tumor without deep myometrial invasion and were aged under 45 years. None of these had ovarian involvement, but they constituted only 5.4% of our study population. Therefore, we tested different suitability criteria for ovarian preservation to be able to include more patients in the study group. Within this context, of 70 patients with grade 1, endometrioid type, <2 cm tumor without deep myometrial invasion, no ovarian metastasis was detected regardless of age. When 88 patients of all ages with endometrioid tumor of any grade without myometrial invasion were considered, no ovarian involvement was seen. Moreover, among 142 patients (19.6% of study population) of any age with grade 1, endometrioid type tumor without deep myometrial invasion, rate of ovarian metastasis was negligible (0.7%) even tumors up to 3 cm in diameter were involved (Table 5).

4. Discussion

The incidence of endometrial cancer diagnosed at younger age has been increasing over time and well-differentiated, early stage tumors associated with favorable prognosis are more common in these patients [8, 9, 12]. Although progestin-based medical therapy with endometrial evaluation every 3–6 months is an option for highly selected patients who desire future fertility, the main approach is usually surgery [19]. Due to long life expectancy in these young patients, quality of life is becoming more of an issue. In this respect, surgical menopause resulting from oophorectomy is associated with serious short and long-term problems including vasomotor symptoms and increased risks of type 2 diabetes and cardiovascular disease [10, 11]. Accordingly, ovarian preservation is becoming a matter of great interest in patients with endometrial cancer. Nevertheless, there are several risks of ovarian preservation in endometrial cancer including risk of occult ovarian metastasis, risk of synchronous endometrial-ovarian cancer, and risk of recurrence from microscopic residues due to ongoing estrogen stimulation [5–7]. Although few studies reported contrary results, there are several studies including two meta-analyses, which showed that the risk of ovarian involvement is very low especially

in low grade and early stage disease and that the preservation of ovaries in these patients does not negatively affect the oncological prognosis in terms of recurrence and mortality [6, 8, 9, 13, 22]. It was also reported that ovarian preservation in young endometrial adenocarcinoma patients is associated with decreased risk of deaths from cardiovascular heart disease and diabetes without increased cancer-related mortality [16].

Several criteria were proposed to be considered for ovarian preservation including upper age limit of 40 or 45 years or being in premenopausal period, having grade 1–2, endometrioid type adenocarcinoma with no signs of extrauterine disease [6, 8, 18, 19]. Also, absence of deep myometrial invasion is another proposed characteristic [8]. However, no uniform agreement exists on this issue and the proposed criteria involves relatively limited number of cases. Most of the findings of the current study are in agreement with the existing evidence. For example, in the current series, 10.5% of patients were premenopausal, 5.4% were under 45 and only 1.9% were under 40 years of age. Therefore, ovarian preservation could be considered in a very limited number of patients if only menopausal status or an upper age limit was regarded. Similarly, some studies focused on oncologic outcomes of patients with ovarian preservation including all age groups without considering menopausal status [15]. Current series identified primary tumor size, grade, histological type, peritoneal cytology, LVSI, cervical involvement, omental metastasis, and lymph node metastasis as factors associated with ovarian metastasis. However, on multivariate analysis, presence of LVSI, cervical spread, omental involvement, and lymph node metastasis were found to be significant independent factors. Nevertheless, these independent factors may usually be reported by final pathology following comprehensive staging procedure. Therefore, we need to define criteria which may safely be used intraoperatively for decision making in the preservation of ovaries. None of our patients had ovarian metastasis if they had grade 1 or 2 endometrioid type disease without deep myometrial invasion and are aged less than 45 years, but these criteria provided ovarian preservation in only 5.4% of our study population. Accordingly, efforts were spent to compose different sets of criteria regardless of age and menopausal status to include more patients. Within this context, ovarian metastasis was absent if endometrioid type tumor of any grade was confined to endometrium while risk of metastasis was negligible if grade 1 tumor without deep myometrial invasion measuring less than 3 cm was detected.

Uterine parameters were solely used to define these novel sets of criteria. These parameters can clearly be identified by preoperative biopsy and intraoperative frozen section evaluation just like those which are used to decide the extent of surgery if ovaries looked normal and gross extrauterine disease is not present [17–19]. Thus, these criteria can easily be used during routine clinical practice wherever and whenever frozen section is available. Also, by using them, ovarian

Table 5. Rates of ovarian involvement when several sets of suitability criteria are used.

Suitability criteria for ovarian preservation	Ovarian metastasis (n, %)		<i>p</i>	% of patients who met the criteria
	Present 66 (9.1)	Absent 659 (90.9)		
Grade 1–2, endometrioid type tumor without deep MI in women aged <45 years				
Criteria met	0 (0.0)	39 (100.0)	0.04	5.4
Criteria unmet	66 (9.6)	620 (90.4)		
Grade 1, endometrioid type, <2 cm tumor without deep MI at any age				
Criteria met	0 (0.0)	70 (100.0)	0.005	9.7
Criteria unmet	66 (10.1)	589 (89.9)		
Any grade, endometrioid type tumor without MI at any age				
Criteria met	0 (0.0)	88 (100.0)	0.02	12.1
Criteria unmet	66 (10.4)	571 (89.6)		
Grade 1, endometrioid type, <3 cm tumor without deep MI at any age				
Criteria met	1 (0.7)	141 (99.3)	<0.001	19.6
Criteria unmet	65 (11.1)	518 (88.9)		

MI, myometrial invasion.

preservation might be a safe option for many more patients with endometrial adenocarcinoma. On the other hand, as shown by multivariate analysis, the risk of ovarian metastasis is high in cases of advanced disease regardless of local uterine factors in accordance with the meta-analysis published by Sun *et al.* [9]. Therefore, when operative exploration reveals gross extrauterine disease, ovarian preservation should not be considered due to poor oncological outcomes and high risk of ovarian metastasis expectancy.

Current study has some potential limitations. First of all, it has a retrospective design with its inherent limitations. Also, current series did not include any patients without oophorectomy which rendered prognostic comparison impossible. Similarly, the oncologic outcomes of the patients as well as the follow-up characteristics were not included as the study only aimed to investigate the variables associated with ovarian metastasis. However, this study clearly demonstrates the characteristics of patients with the presence or absence of ovarian metastasis at the time of the initial surgery. Strengths of the study include high number of cases from division of gynaecologic oncology of a single tertiary center with standard surgical approach, and pathological analysis by dedicated gynaecologic pathologists.

5. Conclusions

In conclusion, ovarian involvement in cases of endometrial carcinoma occurs in less than 10% of cases. Ovarian preservation could be considered in a subgroup of patients with endometrioid adenocarcinoma by using criteria easily defined by preoperative biopsy and intraoperative frozen section evaluation if ovaries looked normal and gross extrauterine disease is not present. Nevertheless, patient counseling should include that ovarian preservation is currently not the standard of care in endometrial adenocarcinoma and safety of this procedure needs further researches. Also, the decision to preserve the ovaries should be discussed preoperatively for

every single patient in multidisciplinary tumor boards and the patients should be informed in detail about potential risks and benefits of such an option before the surgery.

Author contributions

HMB, MCS and MG design the research study. HMB performed the data curation. MCS analyzed the data. The main text of the paper was written by HMB and improved by MCS and NO. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Non-Interventional Clinical Research Ethics Board of Hacettepe University Faculty of Medicine on 9 July 2019 (approval number GO 19/753). Also, per institution's practices, consents were taken from all patients before surgery to use their medical data in medical researches.

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Conflict of interest

The authors declare no conflict of interest. MG is the Editorial board member of this journal, given his role as Editorial board member, he had no involvement in the peer-review of this article and has no access to information regarding its peer-review.

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