Preoperative predictive factor analysis of ovarian malignant involvement in premenopausal patients with clinical stage I endometrioid endometrial carcinoma

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Research article

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Abstract

Background Earlier literature suggests that ovarian preservation in young premenopausal clinical stage I endometrioid endometrial carcinoma patients does not negatively impact prognosis and is a more suitable choice for management of the disease. The main purpose of this study was to clarify the incidence of ovarian malignant involvement in premenopausal clinical stage I endometrioid endometrial carcinoma and further identify potential preoperative predictive factors of ovarian malignant involvement.

Methods Premenopausal patients (≤50 years) with clinical stage I endometrioid endometrial carcinoma subjected to total hysterectomy and bilateral salpingo-oophorectomy with or without pelvic and/or para-aortic lymph node dissection at Women's Hospital, Zhejiang University School of Medicine between 2002 and 2016 were enrolled for study. Patients were excluded in cases of gross extra pelvic disease on examination or imaging and family history of colon or gastrointestinal carcinoma. The included patient population was examined for incidence of ovarian malignant involvement and potential preoperative clinical predictive factors.

Results A total of 511 premenopausal (age≤50 years) patients diagnosed with clinical stage I endometrioid endometrial carcinoma were included for the study. Ovarian malignant involvements were detected in 23 of the patients (4.5%). Kaplan-Meier analysis showed poorer prognoses of patients with ovarian malignant involvement than those without ovarian involvement. Univariate logistic analysis revealed significant association of preoperative imaging of myometrial invasion depth and serum CA125 with prediction of ovarian malignant involvement in patients. Multivariate logistic analysis further validated preoperative imaging of myometrial invasion depth and serum CA125 as independent risk predictors of postoperative ovarian malignant involvement. Receiver operating characteristic (ROC) curves were individually generated for preoperative myometrial invasion depth and serum CA125 as well as a combination of the two factors. The area under the curve (AUC) was 0.772 (95% confidence interval [CI], 0.661–0.884) for combined preoperative myometrial invasion depth and serum CA125.

Conclusions The incidence of ovarian malignant involvement in premenopausal patients with clinical stage I endometrioid endometrial carcinoma was relatively minimal. Preoperative imaging of myometrial invasion depth and serum CA125 were independent risk predictors of ovarian malignant involvement. These findings may facilitate preoperative counseling of patients and informed clinical decision-making on ovarian preservation in these patients.

Background

Endometrial carcinoma is one of the most common gynecological malignancies prevalent in postmenopausal females in the sixth and seventh decades of life (median age of onset, 60 years) [1]. The standard surgical approach for endometrial carcinoma includes total hysterectomy and bilateral salpingo-oophorectomy with or without pelvic and/or para-aortic lymph node dissection, according to the

existence of high-risk factors [1–3]. At present, the incidence of young premenopausal women with endometrial carcinoma is gradually increasing, with 5–30% women aged ≤ 50 years at the time of diagnosis [4]. In the majority of young premenopausal patients, endometrioid endometrial carcinoma is the most common endometrial carcinoma subtype and is usually confined to clinical stage I, namely, located within the corpus uteri without malignant involvement extending beyond the uterus and metastasis to the pelvic and/or para-aortic lymph nodes [4, 5].

Oophorectomy is commonly performed in young premenopausal women with endometrioid endometrial carcinoma in conjunction with hysterectomy, as an estrogen-responsive tumor. In terms of therapeutic benefits, oophorectomy not only decreases estrogen production but also eliminates the occult co-existing involved ovarian metastasis. However, a surgical pathological study for clinical stage I endometrial carcinoma conducted by the Gynecologic Oncology Group reported only a 5% incidence of adnexal involvement, especially in young premenopausal women [6]. The incidence of isolated microscopic ovarian involvement was also uncommon (~1%) [7]. In addition, estrogen deprivation resulting from oophorectomy in young premenopausal women may cause a rapid decline in circulating ovarian estrogen and androgens, leading to increased short- and long-term adverse outcomes, including hot flushes, vaginal atrophy, sleep disorders, cardiovascular disease, osteoporosis, dementia, cognitive impairment, depression and anxiety as well as permanent loss of fertility [3]. Use of this traditional surgical approach is controversial due to occasional ovarian involvement and adverse sequela of estrogen deprivation in young premenopausal patients with clinical stage I endometrioid endometrial carcinoma. However, the safety and feasibility of ovarian preservation in the patient group is of widespread concern. To our knowledge, limited studies have focused on preoperative predictive factors of ovarian malignant involvement in these patients, which may be utilized to determine the optimal surgical approaches for providing maximal therapeutic benefits and further distinguish patients requiring bilateral salpingo-oophorectomy.

Here, we performed a retrospective study on premenopausal patients with clinical stage I endometrioid endometrial carcinoma admitted in Women's Hospital, Zhejiang University School of Medicine, between 2002 and 2016. The incidence of ovarian malignant involvement in these patients and possible preoperative predictive factors were further determined, with a view to optimizing therapeutic management.

Methods

This retrospective study was performed on premenopausal patients (age≤50 years) with clinical stage I endometrioid endometrial carcinoma subjected to total hysterectomy and bilateral salpingo-oophorectomy with or without pelvic and/or para-aortic lymph node dissection from Women's Hospital, Zhejiang University School of Medicine, between January 2002 and December 2016. Patients were identified using hospital tumor registries and an internal database of gynecological carcinoma cases. During this period, 1,978 patients, who were diagnosed with endometrial carcinoma, were admitted in our hospital. CT/MRI imaging was performed to examine myometrial invasion depth and the presence or

absence of enlarged or suspicious paraortic and pelvic nodal disease as well as adnexal involvement. Basis on the preoperative imaging results, patients with suspicious paraortic and pelvic nodal or adnexal involvement were all excluded. Finally, the patients with clinical stage I endometrioid endometrial carcinoma were 1,228 cases. Among them, the numbers of premenopausal patients (age≤50 years) were 518.

All pathological sections were confirmed by two gynecological pathologists (QC and WWW). Ovarian malignant involvement was further determined via postoperative pathologic examination. Among the 518 patients examined, 30 displayed ovarian malignancy involvement, specifically, ovarian endometrioid carcinoma (23 cases), ovarian borderline tumor (three cases), serous papillary carcinoma (two cases), clear cell carcinoma (one case) and mucinous adenocarcinoma (one case). Patients with endometrioid histology of ovary and uterine were included, while other pathological subtypes were excluded. Patients with suspicion of independent synchronous primary uterine and ovarian tumors were also excluded according to the pathological criteria of Ulbright and Roth in 1985 [8] used to distinguish ovarian malignant involvement from independent synchronous endometrial and ovarian carcinoma. Furthermore, an extensive pathological characteristic formulated by Scully et al. [9] was applied to differentiate between uterine endometrial carcinoma with ovarian malignant involvement and independent synchronous primary uterus and ovarian carcinoma. Clinicopathological characteristics favoring primary uterine endometrial tumors with ovarian malignant involvement included histological similarity of tumors, uterine larger size of tumor, presence of uterine atypical endometrial hyperplasia and deep myometrial invasion with direct extension into adnexa and/or lymphovascular invasion. And other evidence of spread from uterine endometrial tumor included bilateral, multinodular, surface involvement of the ovary and absence of endometriosis [9]. Finally, 511 premenopausal patients (≤50 years) with clinical stage I endometrioid endometrial carcinoma were selected for statistical analysis, according to the above admittance standards. Patient demographics and clinicopathological data were obtained through hospital electronic medical records systems and paper charts（Table 1）.

All 511 patients were divided into low risk (n = 193) and sub-high risk groups (n = 318) according to grade 1 or 2 endometrioid endometrial cancer and/or <1/2 myometrial invasion. Pre operative clinicopathological factors (age, preoperative pathological tumor grade, tumor specific site, tumor size, myometrial invasion depth, peritoneal lavage cytology and preoperative serum CA125) were used to evaluate the likelihood of postoperative ovarian malignancy involvement.

All 511 patients enrolled in the study were followed up postoperatively by interview at the clinic or telephone call. Disease-free survival (DFS) and overall survival (OS) rates were calculated from the day of the surgery until recurrence or death. The deadline of follow-up was December 2018. In total, 90 patients (17.6%) were lost to follow-up. The mean follow-up time was 94.56 months (range, 12–202 months). We recorded 26 recurrences (26/421, 6.18%) and 22 deaths (22/421, 5.23%) during this period.

Statistical analysis was performed using SPSS version 23.0. Kaplan-Meier analysis was used to evaluate disease-free and overall survival rate differences between patients with and without ovarian malignant

involvement. We applied univariate and multivariate regression models to analyze preoperative predictive factors for ovarian malignant involvement in clinical stage I endometrioid endometrial carcinoma and plotted ROC curves. Data were considered significant at *p*-values <0.05.

The present study was approved by the Institutional Review Board of Women's Hospital. Informed consent was obtained from all individual participants.

Results

A total of 511 premenopausal (≤50 years) patients were identified. Among these, 193 patients from low risk groups were subjected to total hysterectomy and bilateral salpingo-oophorectomy. A further 318 patients identified with at least one risk factor of sub-high risk groups underwent total hysterectomy and bilateral salpingo-oophorectomy with pelvic and/or para-aortic lymph node dissection. The overall ratio of ovarian malignant involvement was 4.5% (23/511) and the counterparts of low risk and sub-high risk patient groups were 1.04% (n = 2) and 6.6% (n = 21), respectively. The sub-high risk group was associated with a higher rate of ovarian malignancy involvement (P = 0.003) than the low-risk group.

In Kaplan-Meier analysis, patients without ovarian malignant involvement displayed longer disease-free survival (P = 8.0E−6, Figure 1A) and higher five-year survival rates (P = 2.61E−7, Figure 1B) than those with ovarian malignant involvement. Differences were significant between the groups, clearly indicating poorer prognosis of patients with ovarian malignant involvement.

Next, univariate and multivariate regression models were applied to determine preoperative predictive factors for ovarian malignant involvement in clinical stage I endometrioid endometrial carcinoma patients. Univariate logistic analysis disclosed correlations of preoperative imaging of myometrial invasion depth (P = 1.0E−6) and serum CA125 (P = 3.2E−5) with prediction of ovarian malignant involvement in these patients (Table 2). Multivariate logistic analysis further validated preoperative imaging of myometrial invasion depth (P = 0.002) and serum CA125 (P = 3.9E−5) as independent risk predictors of ovarian involvement (Table 3). Other preoperative risk factors, including age at diagnosis, preoperative pathological tumor grade, tumor in specific-site, preoperative tumor size and peritoneal lavage cytology, did not appear associated with ovarian malignant involvement.

Finally, ROC curves were generated with preoperative myometrial invasion depth, serum CA125 and a combination of the two factors. The AUC were 0.692 (95% confidence interval [CI], 0.563 to 0.821) for preoperative myometrial invasion depth alone group and 0.756 (95% confidence interval [CI], 0.624 to 0.888) for preoperative serum CA125 alone group and 0.772 (95% confidence interval [CI], 0.661 to 0.884) for combination group, respectively. The combination of preoperative myometrial invasion depth and serum CA125 (Figure 2) displayed a medium intensity predictive value for postoperative ovarian malignant involvement in premenopausal clinical stage I endometrioid endometrial carcinoma patients.

Discussion

A considerable proportion of premenopausal women are diagnosed with endometrioid endometrial carcinoma, the majority of whom are classified as preoperative clinical stage I [4]. Younger premenopausal patients with clinical I stage endometrioid endometrial cancer have a more favorable prognosis than postmenopausal patients. An earlier large-scale study reported a 5-year disease-specific survival rate of 93% in women younger than 40 years [10]. The higher survival of younger patients may be partly attributed to early-stage and low-grade tumors.

For patients with clinical stage I endometrioid endometrial carcinoma, the traditional surgical approach is total hysterectomy and bilateral salpingo-oophorectomy with or without pelvic and/or para-aortic lymph node dissection according to the existence of high-risk factors. Young premenopausal women with clinical stage I endometrioid endometrial carcinoma subjected to bilateral salpingo-oophorectomy often not only suffer from permanent loss of fertility but also experience climacteric symptoms of decreased estrogen production. Hence, ovarian preservation is a feasible option for this group of patients in the absence of high risk factors. Wright and co-workers confirmed the safety and feasibility of ovarian preservation in a population-based analysis [11]. Consistently, Lee *et al.* [7, 12] reported that ovarian preservation in premenopausal women with early-stage endometrial carcinoma was not associated with poorer outcomes. Another study by Richter and colleagues showed that BSO not only induced better disease-free survival but also did not affect overall survival in young endometrial carcinoma patients [13].

However, occasionally these patients present with occult ovarian malignant involvement, as evident from postoperative detailed pathological inspection. In our analysis, ovarian malignant involvement occurred in 4.5% patients with clinical stage I endometrioid endometrial carcinoma, in keeping with Lin *et al.* [14] who reported ovarian involvement in 5% of their patient group. The ratio of ovarian malignant involvement in low risk patients was 1.04% while patients in the sub-high risk group positive for at least one risk factor showed higher ovarian involvement (6.6%). Data from Kaplan-Meier analysis in the current study showed longer disease-free and higher overall survival rates in patients without ovarian malignant involvement relative to those with ovarian involvement. Ovarian malignant involvement, representing an advanced stage of disease, is generally associated with poorer prognosis. Effective ways to identify patients at higher risk of ovarian malignant involvement and preoperative risk factors that can be used to predict ovarian malignant involvement, especially to distinguish the subgroups of patients suitable for receiving staging surgery for endometrioid endometrial cancer, remains an urgent requirement. The majority of studies to date have focused on postoperative pathological prediction factors, such as myometrial invasion, tumor size, lymphovascular involvement, tumor grade, lymph node metastasis and cervical invasion. Sun and co-workers reported adnexal morphology, lymph node involvement (confirmed via frozen sections) and tumor spread in the peritoneal cavity as the most significant predictors of ovarian involvement, based on data from 203 young women with early-stage endometrial cancer [3]. Chen *et al.* [15] utilized postoperative histological and pathologic data (tumor size, histological type, pathological grade, peritoneal cytology, invasive depth of myometrium, uterine serosal involvement, lymph vascular space invasion, cervical involvement, and adnexa involvement) as effective parameters for distinguishing synchronous primary cancers of endometrium and ovary and endometrial cancer with metastasis to the adnexa. Clinicopathological characteristics (i.e., tumor size, myometrial

invasion, lymphovascular space involvement, lymph node metastasis, tumor grade, cervical invasion and ovarian enlargement ≥5 cm) were used to assess the likelihood of ovarian malignancy by Yoshino and colleagues, who showed the presence of ovarian metastasis in 4.5% patients and identified lymph node metastasis and deep myometrial invasion as significant predictive factors for ovarian metastasis and lymph node metastasis, respectively [16]. Li *et al.* [17] highlighted specific post-operation parameters, such as deeper myometrial invasion, positive lymph node metastasis, positive LVSI, and high histologic grade (G2-G3), associated with ovarian involvement in younger endometrial cancer patients. Furthermore, in multivariate analysis, only deep myometrial invasion was an independent risk factor for ovarian involvement. However, the information is meaningless, because all the above risk factors were evaluated following the operation and not useful for gynecologists prior to surgery. Here, we focused on identifying potential preoperative predictive factors of ovarian malignant involvement, with the aim of providing beneficial guidelines for the appropriate surgical interventions.

Our results suggested that preoperative imaging of myometrial invasion depth and serum CA125 were predictive risk factors of ovarian malignant involvement in premenopausal clinical stage I endometrioid endometrial carcinoma patients, which could aid in preoperative counseling of patients and clinical decision-making for the first time. Univariate and multivariate logistic analyses further validated preoperative imaging of myometrial invasion depth and serum CA125 as independent risk predictors of ovarian involvement in our patient group. Consistently, AUC data showed that combination of preoperative myometrial invasion depth and serum CA125 had medium predictive value for postoperative ovarian malignant involvement to a degree. Preoperative deeper myometrial invasion depth and serum CA125 have been previously identified as prognostic factors in ovarian metastasis [18]. Jiang and colleagues reported that preoperative serum CA125 is an effective predictor of lymph node metastasis in patients with endometrial cancer, in particular, clinical stage I [19]. Analysis of the combined factors also revealed utility as a predictive marker of ovarian malignant involvement to some extent. CA125 has been applied as a tumor marker of ovarian carcinoma since its discovery 30 years ago [20]. A large proportion (80%) of women with primary epithelial ovarian carcinoma and secondary ovarian tumor (70%) are diagnosed based on elevated CA125 levels [21, 22]. Combination of serum CA125 and preoperative myometrial invasion depth may thus present an effective predictive risk factor of postoperative ovarian malignant involvement. Other preoperative risk factors, including age at diagnosis, tumor size [16], peritoneal lavage cytology [23], have no predictive value for ovarian metastasis, the same results with our research.

Our study had a several of limitations that should be acknowledged. One significant factor was the origin of ovarian tumor. Although we set stricter clinicopathological criteria for diagnosis, classification of a part of patients into ovarian malignant involvement or simultaneous uterine and ovarian carcinoma groups was difficult. Moreover, precursor lesions, such as endometrial hyperplasia or concurrent ovarian endometriosis, were not consistently addressed in pathology reports, potentially affecting the final diagnosis. Therefore, novel powerful genetic tools require development for accurate classification of patients displaying complex symptoms in forthcoming research, which would lead to a more accurate research database. Second, large-scale prospective clinical studies are necessary to ascertain whether the

benefits of ovarian preservation outweigh the risks of surgical procedures in clinical stage I endometrioid endometrial carcinoma to reduce bias.

Conclusions

The main purpose of the present study was to identify preoperative predictive factors of ovarian malignant involvement in premenopausal patients with clinical stage I endometrioid endometrial carcinoma. Our results showed that the incidence of ovarian malignant involvement in these patients is relatively minimal. A combination of preoperative myometrial invasion depth and serum CA125 level appeared to have predictive value for postoperative ovarian malignant involvement and may thus aid in informed decision-making on whether or not ovarian preservation should be performed in premenopausal patients with clinical stage I endometrioid endometrial carcinoma.

List Of Abbreviations

ROC: Receiver operating characteristic; AUC: Area under the curve; DFS: Disease-free survival; OS: Overall survival; CA125: cancer antigen 125; FIGO: International Federation of Gynecology and Obstetrics; LVSI: lymph vascular space invasion; LNM: lymph node metastasis

Declarations

Ethics approval and consent to participate

The present study was approved by the Institutional Review Board of Women's Hospital. Informed consent was obtained from all individual participants. (Committee's reference number: 20170197)

Consent for publication

Not applicable

Availability of data and materials

Not applicable

Competing interests:

The authors declare that they have no competing interests.

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Authors' contributions

Yan Feng, Weiguo Lv and Baohua Li analyzed and interpreted all of the patient data. Qin Chen and Wenwen Wang performed the pathological examination of sections, and Qin Chen was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

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Not applicable

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Tables

Table 1. Demographics and clinicopathological data of 511 premenopausal patients with clinical stage I endometrioid endometrial carcinoma

Characteristics	No. of patients	Percentage (%)
Age		
≤40	121	23.68%
40 and ≤50	390	76.32%
FIGO stage		
<II	384	75.15%
≥II	127	24.85%
Differentiation		
Well	363	71.04%
Moderate	107	20.94%
Poor	41	8.02%
Myometrial invasion		
1/2	477	93.34%
≥1/2	34	6.65%
Lymphadenectomy		
Yes	318	62.23%
No	193	37.77%
LNM		
Yes	16	5.03%
No	302	94.97%
Cervical stromal involvement		
Yes	92	18.01%
No	419	81.99%
LVSI		
Yes	15	2.94%
No	496	97.06%
Ovarian involvement		
Yes	23	4.50%
No	488	95.50%

Table 2. Univariate logistic analysis showed the pre-operative predictive factors of ovarian malignant involvement

Characteristics	Ovarian malignant involvement, n (%)		*P*-value
	No	Yes	
Patient age (year)			0.671
	43.93 ± 5.52	43.26 ± 7.41	
Preoperative pathological tumor grade			0.158
Well/moderate	463(90.6)	20(3.9)	
Poor	25(4.9)	3(0.6)	
Tumor in special-site			0.422
No	449(87.9)	20(3.9)	
Yes	39(7.6)	3(0.6)	
Preoperative myometrial invasion depth			1.0E-6
1/2	466(91.2)	14(2.7)	
≥1/2	22(4.3)	9(1.8)	
Preoperative tumor size			0.111
4	407(79.6)	16(3.1)	
≥4	81(15.9)	7(1.4)	
Peritoneal lavage cytology			0.107
Negative	486(95.1)	22(4.3)	
Positive	2(0.4)	1(0.2)	
Preoperative serum CA125 (U/L)			3.2E-5
	22.65(0.4-392)	135.2(1.0-834)	

Table 3. Multivariate logistic analysis showed the pre-operative predictive factors of ovarian malignant involvement

Characteristics	Regression coefficient (B)	Standard error (SE)	χ^2 (Wald)	*P*-value
Preoperative myometrial invasion depth	1.144	0.361	10.017	0.002
Preoperative serum CA125 (U/L)	0.011	0.003	16.940	3.9E-5

Figures

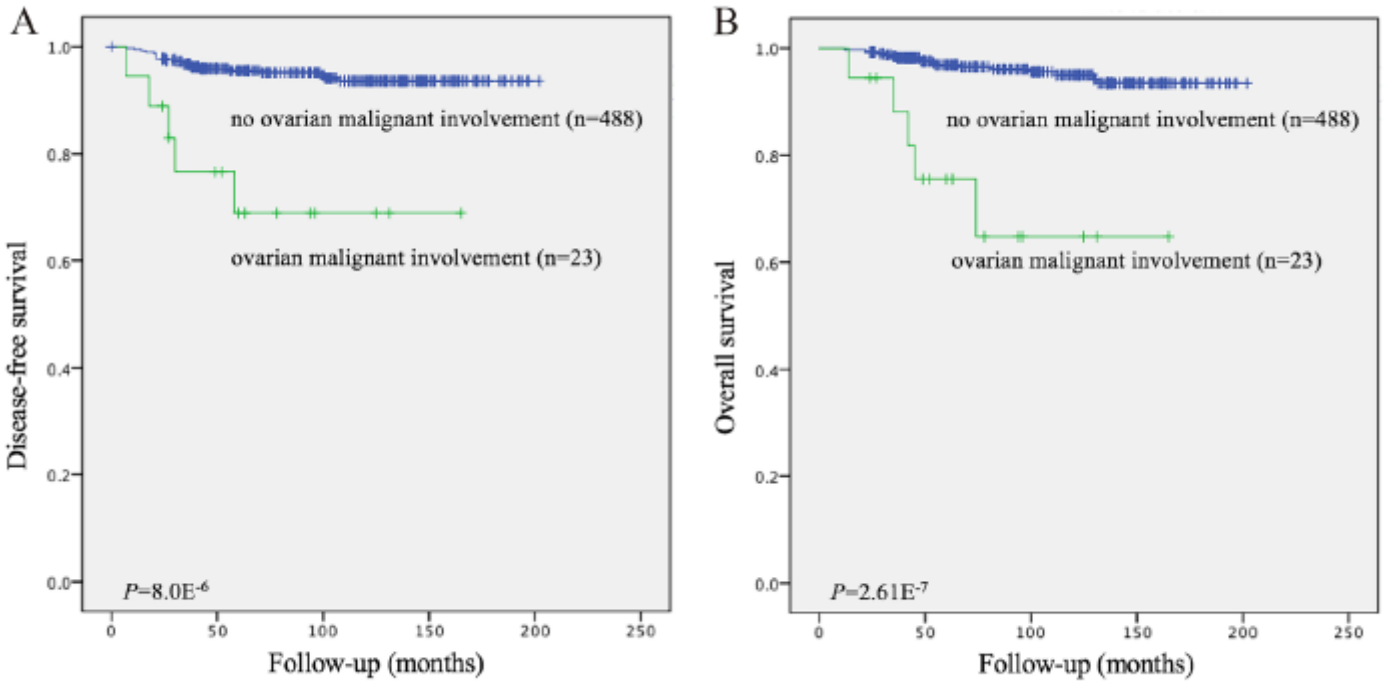

Figure 1

Kaplan-Meier curves showing the relationship between status of ovarian malignant involvement and DFS and overall survival OS in 511 premenopausal patients with clinical stage I endometrioid endometrial carcinoma. The patients with ovarian malignant involvement were significantly associated with shorter DFS (A) and OS (B).

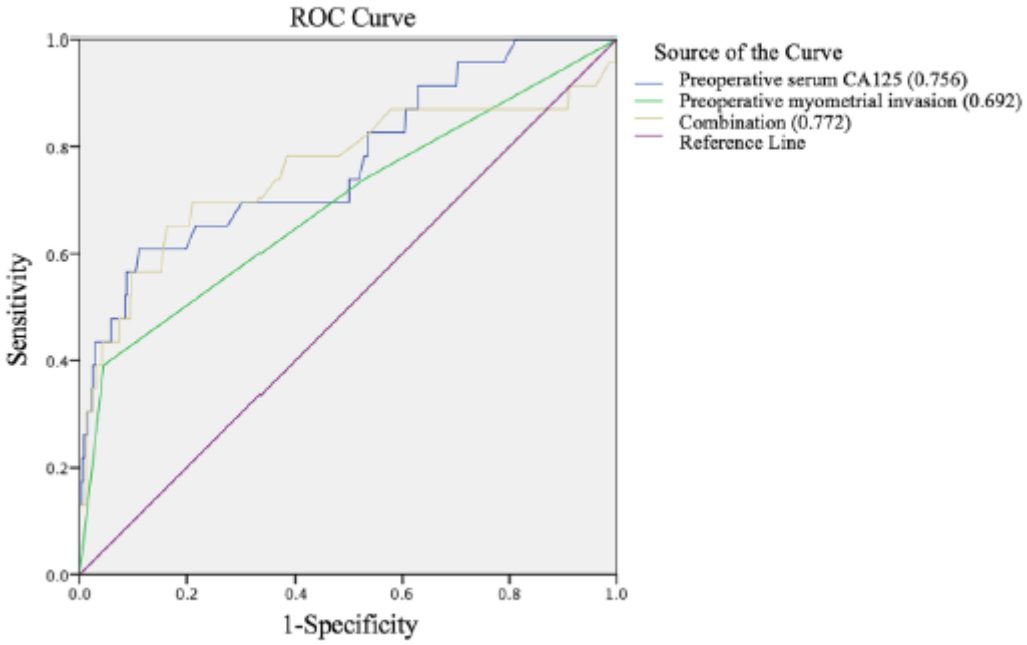

Figure 2

AUC of the multivariate base model (combination of serum CA125 and preoperative myometrial invasion depth) could have medium predictive value for postoperative ovarian malignant involvement in 511 premenopausal patients with clinical stage I endometrioid endometrial carcinoma.