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Adnexal Involvement in Endometrial Cancer: Prognostic Factors and Implications for Ovarian Preservation

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ABSTRACT

Purpose. To determine the risk factors related to adnexal involvement in endometrial cancer (EC) and its implications for ovarian preservation in young women.

Methods. We analyzed a series of 802 patients who were treated at AC Camargo Cancer Center from July 1991 to July 2017. Patients who had peritoneal or systemic dissemination (stage IV) were excluded. Chi square and Fisher's exact tests were used to analyze the correlations between categories and clinicopathological variables. Multivariate analysis was performed by logistic regression.

Results. Forty-nine (6.2%) patients had adnexal involvement—43 (5.4%) ovarian and 24 (2.9%) tubal. After excluding the 14 (28%) cases with suspicious findings, 788 subjects were analyzed and adnexal involvement found in 35 (4.4%) cases. Adnexal involvement was statistically related to non-endometrioid histologies (12.6% vs. 3.1%; $p < 0.001$), lymph node metastasis (17% vs. 2.6%; $p < 0.001$), histological grade 3 tumors (9.4% vs. 2.1%; $p < 0.001$), presence of LVSI (14.2% vs. 2.4%; $p < 0.001$), and deep myometrial invasion ($\geq$ 50%) (10.8% vs. 3.5%; $p < 0.001$). Although age younger than 45 years had higher risk of adnexal involvement, it was not statistically significant (8.9% vs. 4.2%; $p = 0.13$). Seven (14.2%) patients with adnexal involvement were aged < 45 years, 3 of whom (42.8%) had suspicious adnexal masses that were detected before surgery. Notably, all patients aged < 45 years and with adnexal involvement had at least 1 risk factor, such as presence of LVSI, grade 3 disease, node metastasis, or deep myometrial invasion. No patient with clinically normal ovaries and aged under 45 years, with endometrioid grades 1 and 2, superficial myometrial invasion, or node negativity had adnexal involvement.

Conclusions. Ovarian preservation may be considered for patients younger than 45 years old with low-risk EC (grades 1 and 2 tumors, absence of LVSI, and myometrial invasion < 50%).

Endometrial cancer (EC) is the fifth most common cancer among women worldwide, and its incidence is rising in developing countries.[1] Most cases occur in postmenopausal women, at a median age of 61 years.[2] However, approximately 11% are diagnosed before age 50 years, and 5% are diagnosed before age 40 years.[2,3]

Surgery is the cornerstone treatment for endometrial cancer, and surgical staging procedures that include bilateral salpingo-oophorectomy (BSO) are essential for adequate staging and triage for determining the adjuvant therapy in endometrial cancer. The rationale for routine BSO, even in premenopausal patients, is that the ovaries are estrogen producers in potential estrogen-sensitive sites of metastasis.[4]

However, this surgical approach results in the abrupt disruption of hormone levels, with short-term intense menopausal symptoms that can compromise one's quality of life and lead to osteoporosis, metabolic syndrome, and

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cardiovascular disease.[5] Yet, young patients with early-stage tumors are more likely to die from cardiovascular disease than from endometrial cancer.[5] Thus, the decision to preserve the ovaries in premenopausal patients is critical.

Although studies have suggested that BSO and ovarian conservation have similar effects on endometrial mortality in young women with early-stage disease,[6–8] the issue of ovarian conservation remains controversial. Moreover, it is critical to analyze the predictive factors of adnexal involvement to select patients who might safely benefit from ovarian preservation. Our aim was to determine the risk factors that are related to adnexal involvement in endometrial cancer and its implications for ovarian-sparing surgery in young women.

METHODS

We analyzed a series of 887 patients who had surgery including total hysterectomy and BSO for EC from March 1991 to July 2017 at AC Camargo Cancer Center. We excluded 85 patients with stage IV disease (including peritoneal metastasis). We considered adnexal involvement as the presence of ovarian or tubal malignant tumor tissue regardless of the controversial debate on metastatic versus synchronous disease. Cases with neoplastic tissue inside the tubal lumen without invasion were not considered as positive. Moreover, suspicious adnexal involvement was characterized by enlarged solid ovarian lesions found in imaging before or during surgery.

A database was constructed using SPSS, version 20.0 for Mac (SPSS, Inc., Chicago, IL). Chi square and Fisher's exact tests were used to analyze the correlations between categories and clinicopathological variables. Multivariate analysis was performed by logistic regression. For all tests, $p < 0.05$ was considered to be significant.

RESULTS

The median age was 61 years (range, 28–93). Forty-nine (6.2%) patients had adnexal involvement—43 (5.4%) ovarian and 24 (2.9%) tubal disease. Of the patients with adnexal involvement, 14 (28%) had suspicious findings, whereas the imaging was suspicious before surgery in 12 (24%) cases and intraoperative in 2 (4%) cases. We ultimately evaluated 788 patients without suspicious adnexal involvement, and 35 (4.4%) cases had adnexal involvement—9 (25.7%) had only tubal involvement, 19 (54.3%) had only ovarian involvement and 7 (20%) had both ovarian and tubal involvement.

Of 687 (87.2%) endometrioid tumors, 155 (19.6%) were histological FIGO grade 3, and 101 (12.8%) had non-endometrioid histologies (serous, clear cell, or carcinosarcoma). Further, 141 (20.9%) patients experienced lymphovascular space invasion (LVSI), 282 (35.8%) had deep myometrial invasion ($\geq$ 50%), and 100 (15.7%) had lymph node metastasis. The clinical and pathological variables are summarized in Table 1.

The variables that were statistically related to higher risks of adnexal involvement were: non-endometrioid histologies (12.6% vs. 3.1%; $p < 0.001$), lymph node metastasis (17% vs. 2.6%; $p < 0.001$), histological grade 3 tumors (9.4% vs. 2.1%; $p < 0.001$), presence of LVSI (14.2% vs. 2.4%; $p < 0.001$), and deep myometrial invasion (10.8% vs. 3.5%; $p < 0.001$). Although age younger than 45 years had higher risk of adnexal involvement, it was not statistically significant (8.9% vs. 4.2%; $p = 0.13$) (Table 2). In multivariate analysis, non-endometrioid histologies, lymph node metastasis and presence of LVSI remained as independent variables for adnexal involvement (Table 3).

Patients Aged Younger Than 45 Years

Notably, the prevalence of suspicious adnexal lesions for patients aged younger than 45 years was higher compared with $\geq$ 45 years (6.2% vs. 1.5%; $p = 0.046$). Of the 49 patients with adnexal involvement, 7 (14.2%) were age $<$ 45 years, and 3 (42.8%) had suspicious adnexal masses that were detected before surgery. Further, all patients had endometrioid tumors and at least 1 risk factor, such as the presence of LVSI, grade 3 disease, and lymph node metastasis or deep myometrial invasion. No patient with clinically normal ovaries and age under 45 years, endometrioid G1/G2, superficial myometrial invasion, and node negativity had adnexal involvement (Table 4). Three patients with age $\geq$ 45 years with negative risk factors had adnexal involvement, representing only 0.3% of patients.

DISCUSSION

Although most EC occurs in postmenopausal women, the negative impact of BSO is permanent in premenopausal patients, primarily in those aged younger than 45 years. Thus, it is important to determine the risk factors for adnexal involvement and identify the subgroup that is at low risk of adnexal involvement that might benefit from ovarian preservation.

The rationale for salpingo-oophorectomy in the management of EC and the resistance to incorporate ovarian preservation into practice for premenopausal women centers on 2 theoretical concerns. First, the ovaries might be a site of metastatic endometrial cancer or harbor a coexisting primary ovarian tumor that might develop into

TABLE 1 Clinical and pathological characteristics of the 788 patients with stages Ia-IIIc endometrial cancer without suspicious adnexal involvement

Variable	No. of patients	(%)
Age		
< 45 years	45	5.7
≥ 45 years	743	94.3
Ovarian involvement		
No	759	96.3
Yes	29	3.7
Tubal involvement		
No	769	97.6
Yes	19	2.4
Adnexal involvement		
No	753	95.6
Yes	35	4.4
Histologic type		
Endometrioid	687	87.2
Serous	38	4.8
Clear cell	36	4.6
Carcinosarcoma	13	1.6
Mixed (clear cell + serous)	6	0.8
Desdifferentiated	8	1.0
Histologic grade		
Grade 1	313	40
Grade 2	215	27.3
Grade 3[a]	256	32.7
Missing data	5	0.6
LVSI[b]		
No	534	79.1
Yes	141	20.9
Missing data	113	14.3
Myometrial invasion		
< 50%	505	64.2
≥ 50%	282	35.8
Missing data	1	0.1
Type of node staging		
None	136	17.2
Pelvic	246	31.2
Pelvic + Para-aortic	356	45.2
Only sentinel mapping	50	6.3
Lymph node metastasis		
No	536	84.3
Yes	100	15.7

[a]Grade 3: includes 155 endometrioid and 101 non-endometrioid tumors

[b]*LVSI* lymphovascular space invasion

metachronous ovarian cancer. Second, the ovaries produce estrogen, which potentially stimulates microscopic residual endometrial cancer cells.[5,6,9]

In a study of 102 EC patients aged 24 to 45 years, 25% had coexisting ovarian tumors, with 88% considered synchronous ovarian cancer. However, nearly 70% of patients with ovarian involvement had preoperative suspicious imaging.[10] Conversely, more recent studies have reported a lower risk of approximately 5% for ovarian involvement, especially in early-stage EC, with most patients having suspicious involvement in the preoperative imaging or found during surgery.[4,11,12]

Another concern regards the risk of developing metachronous ovarian cancer, especially in young women with EC with an increased hereditary risk.[13,14] In a meta-analysis by Gallos et al.[15] that included patients with EC who had fertility-sparing therapy, a diagnosis of ovarian cancer during follow-up was made in 3.6% of patients. Also, Schmeller et al.[16] reported a risk of ovarian cancer of 5% in patients with Lynch syndrome and ovarian preservation. Moreover, in an analysis of a large retrospective database, Matsuo et al.[9] noted a higher prevalence of subsequent ovarian cancer in patients with EC for those aged < 40 versus ≥ 40 years (2.6% vs. 0.4%; $p = 0.002$). Although it did not contain data on genetic information, most cases had early-stage disease and endometrioid histology, consistent with Lynch syndrome.[13,14] Yet, with a median follow-up of 11 years, there were no deaths from ovarian cancer.

Although we noted a higher risk of adnexal involvement in younger patients, the presence of a suspicious adnexal mass was also frequent in such patients. Moreover, all patients aged under 45 years with adnexal involvement had at least 1 risk factor (LVSI, deep myometrial, grade 3, or node metastasis). Overall, adnexal involvement is a rare event when there are no risk factors, constituting 0.3% of patients, all aged over 50 years. Similarly, Ignatov et al.[17] reported a risk of 0.5% when the same risk factors were absent. Yet, Lin et al.[18] detected 6 (0.8%) cases of microscopic ovarian lesions in a cohort of 759 patients, but all were aged > 50 years, and just 1 (0.1%) had stage IaG1 disease.

Despite the concern that estrogen might stimulate occult EC cells, no study has demonstrated a higher risk of recurrence after ovarian preservation or hormone replacement in early-stage disease. A study by the Korean Gynecologic Oncology Group demonstrated no effect of ovarian conservation on recurrence for stage I and II disease (2.3 vs. 2.5% in 176 of 495).[19] Moreover, several studies, including a phase III trial and a meta-analysis, have argued against the theoretical increase in the risk of recurrence for patients who undergo estrogen replacement for low-risk EC.[20,21]

Nevertheless, there is increasing evidence of the oncologic safety of ovarian conservation. Three studies, retrieved from large databases, support this concept. In a cohort of women aged younger than 45 years from the

TABLE 2 Association between clinical-pathological variables and presence of adnexal involvement for the 788 patients with endometrial cancer without suspicious adnexal involvement

Variable	Adnexal involvement (No. of patients)			
	Category	Absence	Presence	*p*
Age	< 45 years	41	4 (8.9%)	0.13
	≥ 45 years	712	31 (4.2%)	
Histologic type	Endometrioid	656	21 (3.1%)	< 0.001
	Non-endometrioid	97	14 (12.6%)	
LVSI[a]	No	521	13 (2.4%)	< 0.001
	Yes	121	20 (14.2%)	
Myometrial invasion	< 50%	495	18 (3.5%)	< 0.001
	≥ 50%	257	31 (10.8%)	
Lymph node metastasis	No	522	14 (2.6%)	< 0.001
	Yes	83	17 (17.0%)	
Histologic grade	Grades 1 + 2	516	11 (2.1%)	< 0.001
	Grade 3[b]	232	24 (9.4%)	

[a]*LVSI* lymphovascular space invasion

[b]Includes endometrioid G3, and non-endometrioid histologies

TABLE 3 Multivariate analysis (logistic regression) for the risk of adnexal involvement

Variable	Category	Risk of adnexal involvement			
		n	HR	CI	*p*
Histologic type	Endometrioid	476	1.0	Reference	0.017
	Non-endometrioid	95	2.66	1.91–5.96	
LVSI	Absent	442	1.0	Reference	0.005
	Present	129	3.24	1.41–7.44	
Lymph node metastasis	No	474	1.0	Reference	0.004
	Yes	97	3.41	1.49–7.82	

HR hazard ratio, *CI 95%* confidence interval, 95%, *LVSI* lymphovascular space invasion

TABLE 4 Clinical and pathological characteristics of the 7 patients with adnexal involvement and age < 45 years old

Case	Age (years)	Histology	Grade (FIGO)	LVSI[a]	Myometrial invasion (%)	LN[b] metastasis	Suspicious AI[c]
1.	25	Endometrioid	G1	Yes	< 50	No	Yes[d]
2.	31	Endometrioid	G3	Yes	< 50	No	No
3.	37	Endometrioid	G3	No	≥ 50	No	No
4.	41	Endometrioid	G3	Yes	< 50	Yes[e]	No
5.	43	Endometrioid	G1	No	< 50	No	Yes[d]
6.	43	Endometrioid	G1	Yes	< 50	No	Yes[d]
7.	44	Endometrioid	G2	No	< 50	Yes[e]	No

[a]*LVSI* lymphovascular space invasion

[b]*LN* lymph node

[c]*AI* adnexal involvement

[d]Preoperative suspicious imaging

[e]Pelvic node metastasis

SEER database (402 with ovarian preservation among 3269 women), ovarian preservation did not affect cancer-specific or overall survival.[7] Moreover, this database included patients aged under 50 years over a longer period (1242 with ovarian preservation among 12,860). For stage I, grade 1 patients, ovarian conservation was an independent

factor of improved overall survival and was associated with a lower risk of cardiovascular disease. Yet, the cancer-specific survival was similar between groups,[6] supported by results from the National Cancer Database for stage I patients aged younger than 50 years (1121 of 14,527), wherein ovarian conservation did not affect survival.[7]

Overall, our series is comparable in size with the most significant studies on this topic and contributes valuable data. Moreover, our findings can help stratify patients with regard to the risk of adnexal involvement and select those who might benefit from an ovarian-sparing procedure. Unfortunately, it suffers from the inherent biases of a retrospective, single-institution study design. Our data could not evaluate whether low-risk patients will develop a metachronous ovarian tumor during follow-up. Notably, it would be useful to perform genetic testing and counseling when ovarian conservation is considered. An analysis of mismatch repair genes might help better stratify these patients for further evaluation.

In conclusion, certain patients aged less than 45 years old with endometrial cancer have low risk of adnexal involvement. This subset can be identified through a combination of endometrioid histology, low grade (G1/G2), superficial myometrial invasion, negative lymph nodes, and absence of LVSI. When young women with early-stage, low-grade endometrial cancer are counseled regarding ovarian conservation, the risks and benefits of this procedure must be explained.

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