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Can the Ovaries be preserved in Selected Cases of Endometrial Cancer?

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ABSTRACT

Objective: The purpose of this study was to estimate the frequency of ovarian metastasis in patients of endometrial cancer, to examine the clinico- pathological characteristics of cases with ovarian metastasis and to identify associated predictive factors in endometrial adenocarcinoma. **Materials and Methods**: We reviewed the clinical and pathological records of endometrial carcinoma cases diagnosed and treated at our institute between 2007 and 2015. Patient who received primary surgical treatment form the basis of this study. The histopathology reports were studied for information on the following: histology type, grades, depth of myometrial invasion, cervical involvement and lymph node status. Information regarding patient's age was extracted from medical records. These data were then analyzed and compared for relation of ovarian metastasis with various risk factors. **Results**: Total 372 cases of endometrial carcinoma were evaluated. Out of these 32(8.6%) patients had ovarian metastases. No patient under the age of 40 years had ovarian metastasis. 13.3% of patients with more than 50% myometrial invasion and 39.2% of patients with cervix stromal involvement showed ovarian metastasis. There was no ovarian involvement with well differentiated adenocarcinoma as compare to 12.8% with poorly differentiated carcinoma and 38.9% with Non Endometrioid adenocarcinoma. **Conclusion**: The risk of ovarian metastasis in patients without predictable risk factors is minimal. Therefore, it may be possible to preserve ovaries in young women with low grade endometrial carcinoma confined to uterus. However further prospective studies are needed before current recommendation can be changed.

Keywords: Age, endometrial cancer, histopathological findings, ovarian metastasis, ovarian preservation, young patients.

Introduction

Endometrial carcinoma is the most common malignancy of the female genital tract in the western world and the fourth most common malignancy in women after breast, lung and colorectal cancer. Developing countries and Japan have incidence rates four to five times lower than Western industrialized nations with lowest rates being in India and south Asia [1, 2].Most cases (75–85%) of endometrial carcinoma occur between the fifth and seventh decades of life, and 95% occur in patients over 40 years of age. Approximately 20% of patients, however, are diagnosed before menopause, and 5% are diagnosed before the age of 40 years. In the present study 7.79% of cases were below the age of 40 years [3]. Endometrial cancer staging is based on surgery. Standard treatment consists of a total abdominal hysterectomy and bilateral salpingo–oophorectomy (BSO), often accompanied by lymphadenectomy.

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Current recommendation is to remove the ovaries in all cases of endometrial carcinoma regardless of age; The rationale being the 'high' rate of ovarian metastasis, possibility of a coexisting synchronous primary ovarian tumor and possible contribution made by ovarian hormones on microscopic foci of residual endometrial cancer [1, 3].The impact of premature menopause on the quality of life, cardiovascular and bone systems should not be neglected in young patients. Thus, gynecological oncologists face a difficult choice in the management of young patients with endometrial cancer. A few reports from United States and Korea have demonstrated similar survival rates with ovarian preservation in young women with endometrial cancer. However the issue is highly controversial and requires further studies before recommendation for oophrectomy can be changed [4].The purpose of this study was to estimate the frequency of ovarian metastasis in patients of endometrial cancer, to examine the clinico- pathological characteristics of cases with ovarian metastasis and to identify associated predictive factors in endometrial cancer.

Materials & Method

In a retrospective study, we reviewed the clinical and pathological records of endometrial carcinoma cases diagnosed and treated at our institute between 2007 and 2015. Patient who received primary surgical treatment form the basis of this study. Patients who received chemotherapy or radiotherapy as initial treatment were excluded from our study. Also excluded were patients in which complete data was unavailable. Patients with component of mixed mullerian tumor, carcinosarcoma, or endodermal stromal sarcoma were excluded. Inoperable cases, patients with synchronous primary ovarian malignancy and patients of breast malignancy who later developed carcinoma endometrium, were also not included in the study.The majority of patients included had total abdominal hysterectomy, bilateral salpingoophrectomy, bilateral pelvic lymphadenectomy and omental sampling or omentectomy for endometrial carcinoma at our institute. A few patients, who had undergone incomplete surgical treatment (only hysterectomy) elsewhere and then underwent restaging surgery at our institute, were also included in our study, if the original report was available for review. Totally 372 patients of carcinoma of endometrium were included in our study. The original histopathology reports were studied for information on the following prognostic factors: histologic type, grade, depth of myometrial invasion, cervical involvement and lymph node status. Information regarding patient's age was extracted from medical records. These data were than analyzed and compared for rate of ovarian metastasis and also to evaluate associated prognostic factors to predict ovarian metastasis in endometrial carcinoma. The obtained data were compared in Chi-square tests. Probability value less than 0.05 were considered as statistically significant. For statistical purpose endometrioid tumors, endometrioid tumor with squamous differentiation and villoglandular type were all grouped together as Endometrioid adenocarcinoma. Only Endometrioid adenocarcinoma types were further graded as well, moderate and poorly differentiated carcinoma. In present study 21cases had Non Endometrioid histology of which 16 had uterine papillary serous carcinoma (UPSC) and 5 had clear cell. As both of these are very aggressive histology, grading was not applicable.

Results

We analyzed 372 cases of endometrial cancer in the study. Table 1 show that a significant number of women with endometrial carcinoma (7.79%) were under 40 years of age. Thirty two patients (8.6%) were identified to have ovarian metastases. 7.4% of cases above the 60years and 11.5% cases between 50-60 years had ovarian metastasis. No patient under the age of 40 years had ovarian metastasis (Table-2). Out of 372 patients, 351(94.3%) had Endometrioid type, while 21(5.6%) had Non Endometrioid type of adenocarcinoma. Among the Endometrioid group 342 had endometrioid adenocarcinoma, 6 had adenosquamous carcinoma and 3 had villoglandular carcinoma. Non Endometrioid type included 16 cases of uterine papillary serous carcinoma (UPSC) and 5 cases of clear cell carcinoma (Table-3). Twenty nine out of 351cases with Endometrioid type were ≤ 40years, while no patients of Non Endometrioid were ≤ 40years; i.e. all the patients under the age of 40 years had Endometrioid adenocarcinoma. 52.3 %(11/21) of Non Endometrioid type were seen in patient's above 60. Among the Endometrioid adenocarcinoma patient's, grade was compared with age. In patient ≤ 40 years, 68.9 %(20/29) had well differentiated adenocarcinoma and none had poorly differentiated adenocarcinoma. 48.7% (38/78) of poorly differentiated adenocarcinoma were seen in patients above 60(Table-4). Ovarian metastases were seen in 6.8% (24/351) of Endometrioid adenocarcinoma, and 38.9% in Non Endometrioid Adenocarcinoma (Table-5). Statistical analysis of ovarian metastasis in Non-Endometrioid Adenocarcinoma shows p-value of 0.00005, which was statistically significant. Among the Endometrioid adenocarcinoma cases the incidence of

ovarian metastasis was 0%, 11.4% and 12.8% in well, moderately and poorly differentiated adenocarcinoma respectively (Table-6). Absence of ovarian metastasis in 151 cases of well differentiated Endometrioid adenocarcinoma is statistically significant (p-value: 0.00056).Ovarian metastasis were seen in 13.3% of the patient with more than 50% of myometrial invasion (p-value: 0.003) as against only 4.1% of the patient with less than 50% myometrial invasion (Table-7).Ovarian metastases were seen in 6.07% of patients without any cervical involvement and another 6.4% with only cervical epithelial involvement. However 39.2% of patients with cervix stromal involvement showed ovarian metastasis, p-value: 0.000002(Table-8). Of 32 patients with ovarian metastases, 6 patients also had lymph node metastases.

Results:

Table 1: Distribution of cases of endometrial carcinoma according to age

Age	Number of cases
≤40 years	29 (7.79%)
41 -50years	92 (24.7%)
51 – 60 years	130 (34.9%)
>60years	121 (32.5%)
Total cases	372

Table 2: Relationship of age with ovarian metastasis

Age	Total cases	Cases with ovarian metastasis
≤40 yrs	29	0 (0%)
41-50yrs	92	8 (8.6%)
51-60yrs	130	15 (11.5%)
>60yrs	121	9 (7.4%)
Total	372	32 (8.60%)

Table 3: Distribution of cases according to histopathological types

Total cases	372
1. Endometrioid adenocarcinoma	351 (94.3%)
• endometrioid adeno carcinoma	342
• Adenosquamous carcinoma	6
• Villoglandular carcinoma	3
2. Non Endometrioid adenocarcinoma	21 (5.6%)
• Uterine papillary serous carcinoma	16
• Clear cell carcinoma	5

Table 4: Relationship of histology type with age of the patient

Total	Age			
	≤40 years	40-50	50-60	60 above
Endometrioid adenocarcinoma*n=351	29	90	122	110
• Well Differentiated n=151	20	48	48	35
• Moderately Differentiated n=122	9	24	52	37

• Poorly Differentiated n=78	0	18	22	38
Non Endometrioid adenocarcinoma n=21	0	2	8	11

* Grading is done only for Endometrioid adenocarcinoma

Table 5: Relationship of histological types with ovarian metastasis

Histopathological types	Total cases	Cases with ovarian metastasis
1. Endometrioid Adenocarcinoma	351	24 (6.8%)
2. Non-Endometrioid Adenocarcinoma	21	8 (38.9%)

Table 6: Relationship of grade of Endometroid adenocarcinoma with ovarian metastasis

Grade of Endometrioid adenocarcinoma	No. of total cases	Ovarian metastasis
• Well Differentiated	151	0 (0%)
• Moderately Differentiated	122	14 (11.4%)
• Poorly Differentiated	78	10 (12.8%)
Total	351	24

Table 7: Relationship of depth of myometrial invasion with ovarian metastasis

Depth of myometrial invasion	Total cases	Cases with ovarian metastasis
<1/2	192	8 (4.1%)
≥1/2	180	24 (13.3%)

Table 8: Relationship of cervical involvement with ovarian metastasis

Types of Cervical involvment	Total cases	Cases with ovarian metastasis
No cervical Involvement	313	19 (6.07%)
Cervical epithelium	31	2 (6.4%)
Cervical stromal	28	11 (39.2%)

Thirty five patients out of 372 had lymph node metastasis. Of these 6 occurred in patient who had ovarian metastasis.

Discussion

Surgery is the cornerstone of treatment for endometrial carcinoma. Bilateral salpingo-oophrectomy(BSO) regardless of age is currently recommended along with hysterectomy and staging procedure. This treatment policy has not been changed since 1988. The rationale for this is based on the theoretic risks of preserving the ovaries: 'high' rate of ovarian metastasis, the possibility of a coexisting synchronous primary tumor within the ovaries and the possible contribution made by ovarian hormones on pathogenesis of endometrial cancer. However a significant population of women suffering from carcinoma endometrium is premenopausal and about 5% is below the age of 40 years [5]. BSO places them at risk of long term estrogen deprivation. Many trials are being carried out to evaluate the safety of ovarian preservation in young women with endometrial cancer [3, 5].Many studies have found that young women with endometrial cancer have a more favorable prognosis than older patients. Premenopausal women often have low-grade, early-stage tumors that may, in part explain the differential survival. However, there is a lack of information regarding the prognostic factors that predict the risk of ovarian involvement at the time of surgery. Therefore, a largely unanswered question is the safety of ovarian preservation in young women with endometrial cancer. Although prior reports have examined the risk of ovarian metastasis in young women with endometrial cancer, there are not enough data regarding safety of ovarian conservation [6].In our study 7.79% of the endometrial carcinoma patients were below the age of 40 years. Majority of young patients (69.9%) had well differentiated Endometrioid adenocarcinoma. No patient

below the age of 40years had poorly differentiated or Non endometrioid adenocarcinoma (papillary or clear cell carcinoma). In contrast majority of poorly differentiated adenocarcinoma 48.7 %(38/78), and Non endometriod adenocarcinoma cases (11/21) were seen in patients above 60years. This shows that age at diagnosis is an independent prognostic factor. Lee *et al.* showed that women older than 40 years were less likely to have stage I disease and grade I tumors but more likely to have uterine papillary serous histology than women aged 40 years and younger[7] as seen in our study. Their studies also showed that age at diagnosis is an independent prognostic factor for survival. Zaino *et al*. reported 5-year survival rates of 96.3% for patients 50 years or younger [8].In the present study the overall rate of ovarian metastasis in endometrial cancer patient was 8.6%. Although this seems to support the rationale for BSO, when the cases with ovarian metastasis were further analyzed, it was found that, no patients below the age of 40 years had ovarian metastasis. There were no ovarian metastases in well differentiated endometrioid adenocarcinoma. All 32 patients with ovarian metastases had at least one risk factor such as grade, type, myometrial invasion or cervical involvement. While only 6.8% of patient with Endometrioid adenocarcinoma had ovarian metastasis, 38.9% with Non endomerioid adenocarcinoma had ovarian metastasis. This emphasizes the need for detailed and expert review of endometrial biopsy material, preoperatively, especially when planning for ovarian preservation. In the present study 21 cases had Non endometrioid histology of which 16 had uterine papillary serous carcinoma (UPSC) and 5 had clear cell. These are aggressive types of endometrial cancer and have poor prognosis, also confirmed in our study. No patient with well differentiated carcinoma had ovarian metastasis while 11.4% and 12.8% of moderately and poorly differentiated carcinoma had ovarian metastasis respectively. The study conducted by Modaress *et al*. had similar results with no metastasis seen in well differentiated cases [9]. However Lee *et al* showed 4.6% ovarian metastasis in well, 7.9% in moderately and 9.1% in poorly differentiated carcinoma [5, 10]. Cases with more than 50% myometrial invasion showed significant risk of ovarian metastasis, (13.3%) compare to less than 50% myometrial invasion (4.1%). In the study by Gaurin *et al* depth of myometrial invasion was the sole factor predictive for adnexal involvement [11]. When grade and depth of invasion are evaluated separately, the depth of invasion appears to be a more important prognostic factor for ovarian metastasis than the grade of the tumor [8, 12, 13]. Our study showed that the risk of ovarian metastasis was only 6.4% when only cervical epithelium is involved as compared to cervical stromal involvement where the risk was 39.2%. The new FIGO staging also includes only cervical stromal involvement as higher stage. Two mechanisms have been proposed for endometrial carcinoma to develop ovarian metastasis. Firstly, tumor cells can be implanted in ovaries by directly spreading through fallopian tube or uterine muscular layer. The second mechanism of ovarian metastasis is believed to be through lymphatics of uterus. In the second manner of metastasis, positive pelvic lymph nodes, cervical stromal involvement, aggressive histology and negative peritoneal cytology are commonly present, as seen in our case [12]. Lymph node metastases occurred in total 35 cases (9.4%). Out of 32 cases of ovarian metastases patients, six (18.7%) had lymph node involvement. The lymph node status was of importance to determine the prognosis of patients with ovarian metastasis. According to the study by Takeshima *et al* 5 years disease free survival rates were 72% in patients with ovarian metastasis alone, 59.6% in patients with pelvic lymph node metastasis alone and 0% in patients having both ovarian metastasis and lymph node metastasis [10, 12].A Surveillance, Epidemiology and End Results Database (SEER) analysis by Wright *et al*. on the safety of ovarian preservation in premenopausal women with stage I endometrial cancer showed, that ovarian preservation had no effect on either cancer-specific survival or overall survival. They concluded that ovarian preservation in premenopausal women with early-stage disease may be safe and not associated with an increase in cancer-related mortality [6, 9]. Chai *et al*. believe that endometrial carcinoma in patients under 45 are endometrioid adenocarcinoma, related with long term non-allopathic estrogen stimulation, and that most are associated with hyperplasia of endometrium. The prognosis is good, especially for patients younger than 35 [9, 14].In addition to immediate consequence of hot flushes and vaginal atrophy, surgical menopause in young women results in a number of long term sequelae, including an increased risk of cardiovascular disease, osteoporosis and cognitive dysfunction. Thus to avoid the short term and long term consequence of surgical menopause, there is a strong argument for ovarian preservation in young women. [5, 15]In an effort to find out factors predictive of ovarian involvement, we have examined its association with other pathological factors in this study. Similar to GOG results we found that incidence of ovarian metastasis increases with age and in presence of other pathological factors like cervical stromal involvement, deep myometrial involvement, grade 3 of endometrioid adenocarcinoma and aggressive histology [6, 13]. Thus our finding favors ovarian preservation in young woman with well differentiated endometroid adenocarcinma, minimal myometrial involvement and no cervical involvement. Limitations of the present study must be considered when interpreting results. This was a retrospective data analysis which raises the possibility of missing or incomplete data. The pathologist changed over a period of time, leading to the possibility of, interobserver variability in grades and types. The rate of ovarian micrometastasis may have been under evaluated as only one cut section was examined from normal

appearing ovaries rather than multiple cut sections. The safety of ovarian preservation, in early stage of endometrial carcinoma needs confirmation by large scale studies. Ovarian preservation in endometrial cancer patients should be performed cautiously with consideration of patient's age and patient's desire for ovarian preservation after fully informed explanation of potential risks. Follow up of patients who have undergone ovarian preservation should be extended to rule out the possibility of subsequent ovarian metastasis [5, 6, 10, 12].

Conclusion

According to our study ovarian preservation may be offered to selected young patients who want to retain ovarian function, with a preoperative histological diagnosis of well differentiated endometrioid type, disease confined to uterus, myometrial invasion limited to less than one half of the myometrium, no cervical involvement and no gross pre or intraoperative abnormality in ovaries. However this must be confirmed with large, multicentric, prospective studies. Pathologists must be requested to take multiple sections of normal appearing ovaries in endometrial carcinoma patients to rule out micrometastases. Ovarian preservation in endometrial cancer should be considered as an exception, and proposed as an individualized plan of care for patients, with strict eligibility criteria.

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