Ca 19-9 Could Predict both Advanced Disease and Nodal Involvement in Primary Mucinous Endometrial Cancers

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ABSTRACT

Objective: Mucinous endometrial carcinoma is a rare disease. A study to evaluate and find predictive factors of mucinous endometrial carcinoma for advanced disease and nodal involvement was performed.

Methods: Patients who were operated at the Gynecologic Oncology Department of Zekai Tahir Burak Women's Health, Education and Research Hospital between January 2006 and January 2013 were evaluated and patients with primary mucinous endometrial carcinoma were retrospectively analysed.

Results: A total of 16 primary mucinous endometrial carcinoma patients were detected. Patients were evaluated into two groups according to stage. Group 1 was consisted of stage IA patients and group 2 was consisted of patients with higher stages than 1A (advanced disease). Twelve patients (75%) were stage IA whereas four patients (25%) were having higher than stage IA disease. Lymph node metastasis and LVSI were significantly positive in advanced disease ($p = 0.011$ and $p = 0.01$, respectively). Ca 125 and Ca 19-9 levels were also significantly elevated in patients with advanced disease ($p = 0.021$ and $p = 0.039$). On the other hand only Ca 19-9 was significantly elevated in the patients with nodal metastasis.

Conclusion: Preoperative work up of Ca-19.9 could predict both advanced disease and lymph node metastasis for mucinous endometrial cancers.

Keywords: Ca-19.9, stage mucinous endometrial cancer, lymph node

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INTRODUCTION

Endometrial cancer is the most common gynaecologic malignancy. Endometrioid histology is the main type of this carcinoma and is associated with a good prognosis and long survival.

They are generally detected in early stages without any nodal involvement and metastasis. Despite the rarity of non-endometrioid type, they behave aggressively and constitute the major part of recurrences and deaths. Extra uterine disease is commonly detected with them, nodal involvement may also exist (1, 2). Mucinous endometrial carcinoma is one of the non-endometrioid carcinomas and it is less than 10% of all endometrial cancers (3).

Tumour stage, grade, histologic type and dept of myometrial invasion are important prognostic factors of endometrial cancer (4). Lymph node metastasis could upstage a patient and has a direct role on survival. It has been previously mentioned that mucinous histology is also a risk factor for lymph node metastasis (5). Moreover Tumour markers are generally evaluated in gynecologic oncology practice, nevertheless they have a limited role on the management and follow-up (6). In that clinical setting a study to evaluate primary mucinous endometrial cancers was performed within clinicopathologic parameters.

MATERIALS AND METHODS

This institutional ethical board approved study was performed at Zekai Tahir Burak Women's Health, Education and Research Hospital, Turkey. Patients who were operated at the Gynecologic Oncology Department between January 2006 and January 2013 were evaluated and patients with primary mucinous endometrial carcinoma were retrospectively analysed.

Mucinous endometrial carcinoma was defined if the intracytoplasmic mucin collection is more than 50% of total tumour cell population. These cells are positive for mucicarmine and periodic acid-Schiff stain (7, 8). We excluded cases with less than 50%

mucinous architecture. Patient's age, menopausal status, parity, symptom, body mass index (BMI), stage, grade, myometrial invasion, cervical involvement, tumour diameter, lymphovascular space invasion (LVSI), lymph node count-metastasis, peritoneal cytology, Ca 125 and Ca 19-9 values were considered for analysis.

All patients underwent hysterectomy, bilateral salpingo-oophorectomy, pelvic-araaortic lymphadenectomy and omentectomy. The International Federation of Gynecology and Obstetrics (FIGO) staging system for endometrial carcinoma, 2009 was performed for clinical staging. All the operations were performed by certified gynaecological oncologists and pathology specimes were interpreted by senior pathologists on gynaecological oncology.

The statistical analyses were performed by using Statistics Package for Social Sciences version 17.0 (SPSS, Chicago, IL). The Chi-squared and Fisher's exact tests were used to analyse nominal variables in the form of frequency tables. Non-normally distributed metric variables were analysed by Mann-Whitney U test; *p*-values of < 0.05 were considered statistically significant. Values were expressed as mean ± SD, unless stated otherwise.

RESULTS

A total of 16 primary mucinous endometrial carcinoma patients were detected. The incidence of mucinous endometrial cancer out of 658 endometrial carcinoma patients is 2.43%. Median age of the patients was 60 and 12 patients (75%) were postmenopausal. Vaginal bleeding (n = 12, 75%) was the main symptom and pelvic pain was the most common accompanying symptom. Patients were evaluated into two groups according to stage. Group 1 was consisted of stage IA patients and group 2 was consisted of patients with higher stages than 1A (advanced disease). Twelve patients (75%) were stage IA whereas four patients (25%) were having higher than stage IA disease (2 patients (12.5%) stage IB, 2 patients (12.5%) stage

IIIC2). Mean age, BMI, parity, tumour diameter, lymph node count and menopausal status was not significantly different between the groups (Table 1). Lymph node metastasis and LVSI were significantly positive in advanced disease (p = 0.011 and p = 0.01, respectively). Ca 125 and Ca 19-9 levels were also significantly elevated in patients with advanced disease (p = 0.021 and p = 0.039) [Table 1].

Table. 1: Clinicopathological characteristics of patients according to stage.

Characteristics	**Stage IA (n = 12)**	**> Stage IA (n = 4)**	***p*-value**
Age	57.1 ± 5.4	58.7 ± 11.7	> 0.05
BMI	31.3 ± 4.6	32.4 ± 5.7	> 0.05
Parity	3.3 ± 1.8	4.1 ± 2.3	> 0.05
Postmenopausal	9 (75%)	3 (75%)	> 0.05
Tumour diameter	1.4 ± 0.7	2.1 ± 1.5	> 0.05
Pelvic lymph node Count	47.5 ± 23.1	44.0 ± 15.7	> 0.05
Paraaortic lymph node Count	19.0 ± 10.1	17.7 ± 3.5	> 0.05
Lymph node metastasis	0 (0%)	2 (50%)	0.011
LVSI	1 (8.3%)	3 (75%)	0.01
Ca-125	17.4 ± 13.5	48.5 ± 31.4	0.021
Ca-19.9	19.0 ± 11.3	88.2 ± 76.3	0.039

Lymph node metastasis was detected in two patients (12.5%). One of these patients was with isolated paraaortic lymph node metastasis and the other one was with pelvic and paraaortic lymph node metastasis. Only Ca 19-9 was significantly elevated in the patients with nodal metastasis (p = 0.026). The other parameters were similar and non-significant (Table 2).

Table. 2: Tumour marker levels of patients according to lymph node metastasis.

Characteristics	**Negative lymph node metastasis (n = 14)**	**Positive lymp node metastasis (n = 2)**	***p***
Ca-125	20.2 ± 15.3	50.9 ± 40.3	0.08
Ca-19.9	18.6 ± 12.1	148.5 ± 51.6	0.026

DISCUSSION

Mucinous metaplasia of endometrial glands shows variable degrees of epithelial change with or without intraglandular micropapillary features. Additionally a complex glandular architecture similar to low grade mucinous adenocarcinoma could also be seen (9). Lesions with these histopathologic features could be a precancerous lesion of mucinous adenocarcinoma (10). Cytologic atypia is an important predictor of malignancy risk for mucinous proliferations (11). In that clinical setting care should be taken during evaluation of these patients.

Mucinous endometrial carcinoma is a rare histologic subtype of endometrial cancer. Because of the limited number of studies, only retrospective small cohorts shape the clinical management. Stage and grade are the most important prognostic factors. Mucinous tumours generally present in elderly. Mucinous endometrial carcinomas may present as an advanced stage tumour (2). However Jalloul *et al* (12) had reported mucinous endometrial carcinomas as low grade and early stage tumours. Nevertheless the frequency of deep myometrial invasion should not be underestimated for mucinous endometrial cancers (13). Within this study 12 patients (75%) were stage IA and 10 patients (62.5%) were in grade 1 histology.

Musa *et al* (5) performed a case control study with mucinous and endometrioid endometrial carcinomas and found mucinous histology as an independent predictor of lymph

node metastasis. However the risk of deep myometrial invasion do not increase. A recent analysis of SEER (surveillance, epidemiology, and end results) analysed 103 097 endometrioid endometrial adenocarcinoma patients (98.5%) and 1562 mucinous endometrial adenocarcinoma patients (1.5%) and found extent of nodal metastasis higher for patients with a mucinous carcinoma (3). Despite these findings survival period for mucinous endometrial carcinoma patients do not decrease after stage matched analysis (2). Surveillance, epidemiology, and end results database also showed that mucinous histology has no effect on cancer specific survival (3).

Disease specific survival for mucinous endometrial carcinoma patients with hysterectomy and pelvic-paraaortic lymphadenectomy was not different from endometrioid endometrial cancer patients according to SEER analysis. Despite a low grade disease, mucinous endometrial cancers could have lymphatic metastasis. On the other hand lymphadenectomy is controversial for early stage and low grade cancers (3, 14).

In this study lymph node metastasis and LVSI were more common in the advanced stage group however we performed retroperitoneal systematic lymphadenectomy to all patients as a standart surgical theraphy. There is a debate on the best surgical practice for early stage mucinous endometrial carcinoma patients. Owusu-Darko *et al* (15) performed a case control study and did not find any difference between mucinous endometrial carcinoma and endometrioid endometrial carcinoma on overall survival and disease free survival when treated with hysterectomy and bilateral salpingo-oophorectomy. Gungorduk *et al* (16) also did not find any difference regarding the survival analysis of mucinous and endometrioid endometrial cancers however they suggested routine retroperitoneal lymphadenectomy for mucinous endometrial carcinoma patients because of the increased incidence of lymph node matastasis.

Despite the tendency towards lymphatic dissemination, the risk of myometrial invasion do not increase significantly in mucinous endometrial carcinomas (7) and it is a less aggressive form of endometrial cancer with similar management options like endometrioid endometrial carcinoma (3). Whorley *et al* (17) showed an increased incidence of myometrial invasion for patients with mucinous endometrial carcinoma nevertheless the incidence of deep myometrial invasion was not higher; that was also proved by Musa *et al* (5). They did not find any significant difference for LVSI, in contrast for this study LVSI was more common in the advanced stage group.

Tumour markers are commonly used parameters of gynaecologic oncology practice. They have a role during the detection and monitoring of malignancies, especially ovarian cancer. Ca-19.9 is a monosialoganglioside, associated with mucins in gastrointestinal adenocarcinomas (18) and Ca-125 is known to be expressed in coelomic epithelium; Mullerian epithelium, peritoneum, pleura and pericardium (19). The functional rationale for the usage of these markers has been proposed in various studies previously. There are many ongoing studies related with endometrial cancer and tumour markers. We found Ca-125 and Ca-19.9 significantly elevated in the group of advanced disease patients however the only significant parameter for patients with lymph node metastasis was Ca-19.9. Neunteufel *et al* (20) reported an association between well differentiated endometrial adenocarcinomas and Ca-19.9 positivity. Duk *et al* (21) had proposed a significance between stage and Ca-125 for endometrial cancers. Kanat-Pektas *et al* (22) defined elevated levels of Ca-125 and Ca-19.9 for endometrial carcinoma that was also correlated with tumour stage; however non-selective elevations of these markers with various benign and malignant situations draw the poorness of these markers. Baser *et al* (23) found Ca-125, Ca-19.9 and Ca-15.3 significant in the prediction of postoperative adjuvant therapy need. Especially Ca-125 was important during this management. Since the progressive increase of Ca-125 from well to

poor differentiated carcinomas, Cherchi *et al* (24) defined Ca-125 as the most valuable marker for endometrial carcinomas.

The data regarding the mucinous endometrial carcinomas are limited. The need of the tumour markers for the prediction of prognosis and prognosticators is controversial and there are also questionnaires related with sensitivity and specificity. On the other hand Ca-125 is a well-known marker with a wide literature data. As far as this study Ca-19.9 is proposed as a marker for mucinous endometrial carcinomas and we have not find a similar research.

As a conclusion, mucinous endometrial carcinomas are generally low grade and low stage cancers with an increased risk of nodal metastasis. Preoperative work-up of Ca-19.9 could predict both advanced disease and lymph node metastasis for these tumours.

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