ORIGINAL ARTICLE

CA 19-9 Could Predict Both Advanced Disease and Nodal Involvement in Primary Mucinous Endometrial Cancers*

I Selcuk[1], S Bas[1], M Oz[1], E Ozgu[1], M Turker[2], H Yalcin[1], T Gungor[1,3]

ABSTRACT

Objective: *As 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 on at the Gynaecologic 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 based on two groups, according to stage. Group 1 consisted of stage IA patients and group 2 consisted of patients with higher stages than 1A (advanced disease). Twelve patients (75%) were stage IA whereas four patients (25%) had higher than stage IA disease. Lymph node metastasis and lymphovascular space invasion 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: *Pre-operative work-up of CA-19.9 could predict both advanced disease and lymph node metastasis for mucinous endometrial cancers.*

Keywords: Endometrial cancer, lymph node, lymphovascular space invasion, mucinous tumour, tumour markers.

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. Endometrial cancer is generally detected in the early stages, without any nodal involvement and metastasis. Despite the rarity of the non-endometrioid type, this type behaves aggressively and constitutes the major part of recurrences and deaths. Extrauterine disease is commonly detected with the non-endometrioid type and nodal involvement may also exist (1, 2). Mucinous endometrial carcinoma is one of the non-endometrioid carcinomas and is less than 10% of all endometrial cancers (3).

Tumour stage, grade, histologic type and depth of myometrial invasion are important prognostic factors of endometrial cancer (4). Lymph node metastasis could upstage a patient and has a direct role in 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 gynaecologic oncology practice, and have a role in the management and follow-up (6). In that clinical setting, a

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From: [1]Gynaecologic Oncology Unit, Zekai Tahir Burak Women's Health, Education and Research Hospital, Ankara, Turkey, [2]Pathology Unit, Zekai Tahir Burak Women's Health, Education and Research Hospital, Ankara, Turkey and [3]Department of Obstetrics and Gynaecology, Faculty of Medicine, Hitit University, Corum, Turkey.

Correspondence: Dr Ilker Selcuk, Gynaecologic Oncology Unit, Zekai Tahir Burak Women's Health, Education and Research Hospital, 06030 Ankara, Turkey.
Email: ilkerselcukmd@hotmail.com

study to evaluate primary mucinous endometrial cancers was performed within clinicopathologic parameters.

SUBJECTS 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 Gynaecologic 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 the total tumour cell population. These cells are positive for mucicarmine and periodic acid-Schiff stain (7, 8). We excluded cases with less than 50% of 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, cancer antigen (CA) 125, and CA 19-9 values were considered for analysis.

All patients underwent hysterectomy, bilateral salpingo-oophorectomy, pelvic-paraaortic lymphadenectomy and omentectomy. The International Federation of Gynaecology 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 specimens were interpreted by senior pathologists in gynaecological oncology.

The statistical analyses were performed by using the Statistics Package for the Social Sciences version 17.0 (SPSS, Chicago, IL, USA). The Chi-square and Fisher's exact tests were used to analyse nominal variables in the form of frequency tables. Non-nominally distributed metric variables were analysed by the Mann–Whitney *U* test. *p*-values < 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%. The median age of the patients was 60, and 12 (75%) were post-menopausal. Vaginal bleeding (n = 12, 75%) was the main symptom and pelvic pain was the most common accompanying symptom. Patients were evaluated based on two groups, according to the stage. Group 1 consisted of stage IA patients, and group 2 consisted of patients with higher stages than 1A (advanced disease). Twelve patients (75%) were stage IA, four patients (25%) had higher than stage IA disease; two patients (12.5%) were stage IB, and two patients (12.5%) were stage IIIC (2). Mean age, BMI, parity, tumour diameter, lymph node count, and menopausal status were 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

BMI = body mass index; LVSI = lymphovascular space invasion.

Lymph node metastasis was detected in two patients (12.5%). One of these patients had isolated paraaortic lymph node metastasis and the other one had pelvic and para-aortic 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 not significant (Table 2).

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

Characteristics	Negative lymph node metastasis (n = 14)	Positive lymph 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 the endometrial glands showed 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 precancerous lesions 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 the 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 the elderly people. 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 does not increase. A recent analysis of surveillance, epidemiology, and end results (SEER) analysed 103 097 endometrioid endometrial adenocarcinoma patients (98.5%), and 1562 mucinous endometrial adenocarcinoma patients (1.5%), and found the extent of nodal metastasis higher for patients with a mucinous carcinoma (3). Despite these findings, the survival period for mucinous endometrial carcinoma patients does not decrease after stage-matched analysis (2). The SEER database also showed that mucinous histology does not affect 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 the 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 standard surgical therapy. 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 metastasis. Despite the tendency towards lymphatic dissemination, the risk of myometrial invasion does not increase significantly in mucinous endometrial carcinomas (7). It is a less aggressive form of endometrial cancer with similar management options as 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, a finding also reported by Musa *et al*. (5). They did not find any significant difference for LVSI. In contrast to that study, LVSI was more common in the advanced stage group of our patient cohort.

Tumour markers are commonly used parameters of gynaecologic oncology practice. They play a role in 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 the coelomic epithelium, including the Mullerian epithelium, peritoneum, pleura, and pericardium (19). The functional rationale for the use of these markers has been proposed in various studies previously. There are many ongoing studies related to 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) 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 show the poorness of these markers. Baser *et al*. (23) found CA-125, CA-19.9, and CA-15.3 were significant in predicting postoperative adjuvant therapy need. CA-125 was especially important during this

management. Since the progressive increase of CA-125 from well to poorly differentiated carcinomas, Cherchi *et al*. (24) defined CA-125 as the most valuable marker for endometrial carcinomas.

The data regarding mucinous endometrial carcinomas are limited. The need of the tumour markers for the prediction of prognosis and prognosticators is controversial, and there is also controversy regarding sensitivity and specificity. On the other hand, CA-125 is a well-known marker with extensive literature data. In this article, CA-19.9 is proposed as a marker for mucinous endometrial carcinomas, and we have not found similar research.

CONCLUSION

In conclusion, mucinous endometrial carcinomas are generally low-grade and low-stage cancers with an increased risk of nodal metastasis. Pre-operative workup of CA-19.9 could predict both advanced disease and lymph node metastasis for these tumours.

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