RESEARCH ARTICLE

Predicting Lympho-Vascular Space Invasion in Endometrial Cancers with Mucinous Carcinomatous Components

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Abstract

Objective: To determine the predictors of lympho-vascular space invasion (LVSI) in endometrial cancers which contain mucinous carcinomatous histology. **Materials and Methods:** Clinical and histopathological data of endometrial carcinomas with a mucinous carcinomatous component diagnosed between January 2007 and January 2014 at the Gynecologic Oncology Department of Zekai Tahir Burak Women's Health Education and Research Hospital were reviewed retrospectively. **Results:** Twelve patients (25.5%) were positive for LVSI and 35 (74.5%) patients were negative. Patients with LVSI were mostly staged higher than 1A. Mean age, BMI and parity were not significantly different between patient groups. Larger tumor diameter (≥2cm) (p=0.04) and elevated Ca125 and Ca-19.9 (p=0.01) levels were significant for predicting LVSI. We also found >1/2 myometrial invasion (p<0.001), cervical stromal involvement (p=0.002) and higher grade (2-3) (p=0.001) significant for predicting LVSI. In multivariate analysis we found only grade significant for predicting LVSI. **Conclusions:** Especially grade of tumor is a crucial factor for determining LVSI in endometrial cancers with mucinous carcinomatous components.

Keywords: Endometrial - carcinoma - mucinous - grade - LVSI

Introduction

Endometrial cancer (EC) is the most common gynecologic malignancy (Wilairat and Benjapibal, 2012; Siegel et al., 2013). The two distinct histologic types of EC; Type 1 and Type 2 show independent features. Type 1 cancers are more common and generally detected in early stages with a favorable prognosis however Type 2 cancers are rarely seen and behave aggressively (Patsavas et al., 2011). Type 1 endometrial cancer patients are generally younger than Type 2 carcinoma patients and they are mostly obese. Apart from that an additional primary tumor, especially breast cancer could accompany Type 2 carcinomas (Felix et al., 2010). However Type1-endometrioid endometrium tumors could be detected synchronously with ovarian tumors rather than other malignities (Natee et al., 2006; Gungor et al., 2009). Mucinous carcinoma of endometrium is categorized under Type 2 (non-endometrioid) cancers and they are less than 5% of endometrial cancers (Rauh et al., 2014). Mucinous carcinomas are generally detected in early stages and they are mostly grade 1 tumors (Melhem and Tobon, 1987).

Histopathologic features of endometrial carcinomas are especially important and would categorize the tumor for a high risk disease (Binesh et al., 2014). Histologic subtype, grade, myometrial invasion, cervical stromal invasion and lymphovascular space invasion (LVSI) are crucial findings for determining a high stage disease (Taskiran et al., 2006). Thus we evaluated the markers for predicting LVSI in endometrial cancer patients who are with a mucinous carcinomatous component.

Materials and Methods

The clinical and histopathological data of patients who underwent surgical staging for endometrial carcinoma between January 2007 and January 2014 at the Gynecologic Oncology Department of Zekai Tahir Burak Women's Health Education and Research Hospital were reviewed retrospectively. The study was approved by the institutional ethics committee of hospital.

The total number of EC patients at that time period was 643. Mucinous carcinomatous component was detected in 47 patients (7.3%); of them 31 patients were having endometrioid type of carcinoma pattern additionally and 16 patients were having only mucinous type of carcinoma.

Total abdominal hysterectomy, bilateral salpingo-oophorectomy, pelvic-paraaortic lymphadenectomy

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Table 1. Clinical Features of Patients

Characteristics		number (%)
Mean Age		56.64±6.3
Mean BMI (kg/m^2)		32.4±2.7
Mean parity		3.36±1.6
Mean pelvic lymph node count		43.6±18.4
Mean para-aortic LN count		19.6±8.5
Mean tumor diameter	(cm)	1.8±1.3
Stage		
	IA	32 (68%)
	IB	5 (10.6%)
	II	4 (8.5%)
	IIIC2	6 (12.7)
Elevated Ca-125 (IU/mL)		10 (21.2%)
Elevated Ca-19.9 (IU/mL)		13 (27.6%)

and omentectomy was the standard surgical procedure. Body mass index (BMI), stage, grade, cervical stromal involvement, tumor diameter, tumor markers, LVSI, symptoms, pelvic and paraaortic lymph node counts, parity and peritoneal cytology were reviewed from medical records. Staging was determined according to International Federation of Gynecology and Obstetrics Staging Criteria, 2009.

Statistical analyses were performed with SPSS for Windows version 17.0 statistical package (SPSS Inc., Chicago, IL, USA). Chi square test or independent samples t test, Mann-Whitney U test were used for the analysis and which found significant were analysed with logistic regression test. A $p<0.05$ was set for statistical significance.

Results

A total of 47 EC patients with mucinous carcinomatous component were evaluated. Mean age of patients was 56.64±6.3 years (minimum 45, maximum 74); mean parity 3.36±1.6; mean BMI 32.4±2.7 kg/m^2; mean pelvic lymph node (LN) count 43.6±18.4; mean para-aortic LN count 19.6±8.5 and mean tumor diameter was 1.8±1.3 cm. Most of the patients were in menopausal status (n=37, 78.7%) however ten patients were premenopausal. Only one patient (2.1%) was nulliparous. Postmenopausal bleeding was the most common symptom. Thirty-two patients

(68%) were stage 1A; five patients (10.6%) were stage 1B, four patients (8.5%) were stage 2 and six patients (12.7%) were stage 3C2. Thirty-one patients (65.9%) were having a grade 1 tumor, and 25 of them were stage 1A. Ascites was not detected within any patient. Ca125 level (0-35 U/mL) was elevated in 10 patients (21.2%); Ca19-9 level (0-37 U/mL) was elevated in 13 patients (27.6%) and CEA level (0-5 ng/mL) was elevated in one patient. Table 1 shows the clinical features of patients. Diabetes and hypertension were detected in 20 (42.5%) and 29 (61.7%) patients respectively.

Twelve patients (25.5%) were with LVSI however 35 (74.5%) patients were without LVSI. Patients with LVSI were mostly staged higher than 1A; 3 patients (25%) were stage 1B, 2 patients (16.6%) were stage 2 and 4 patients (33.3%) were stage 3C2. Nine of these 12 patients (75%) were having a disease higher than grade 1, six (50%) of them were with cervical stromal involvement and nine patients (75%) were having a myometrial invasion greater than 1/2. Mean age, BMI and parity were not significantly different between patient groups. Larger tumor diameter (≥2cm) (p=0.04) and elevated Ca125 and Ca-19.9 (p=0.01) levels were significant for predicting LVSI. We also found >1/2 myometrial invasion (p<0.001), cervical stromal involvement (p=0.002) and higher grade (2-3) (p=0.001) significant for predicting LVSI. Table 2 shows the discrimination of patients according to LVSI.

Only one patient of positive LVSI group was with malignant peritoneal cytology. She was staged 3C2. However malignant peritoneal cytology was not predictive for LVSI (p=0.255). In multivariate analysis we found only grade significant for predicting LVSI (odds ratio: 15.5, 95% confidence interval 1.9-67.9, p=0.004).

Discussion

Mucinous adenocarcinoma of endometrium is a rare histologic type of EC that there are limited studies regarding this subject in the literature. During the time period of study the prevalence of mucinous histology as an endometrial carcinoma was 7.3%. More than one half of the cell population of the tumor must contain periodic acid Schiff-positive diastase-resistant intracytoplasmic mucin to define it as mucinous carcinoma (Jalloul et al., 2012). Mean age of patients was 56.64±6.3 years, patients

Table 2. Discrimination of Patients According to LVSI

Characteristics	LVSI (+) n (%)	LVSI (-) n (%)	p value
Patient numbers	12 (25.5%)	35 (74.5%)	
Stage			
IA	3 (25%)	29 (82.8%)	
IB	3 (25%)	2 (5.7%)	
II	2 (16.6)	2 (5.7%)	
IIIC2	4 (33.3%)	2 (5.7%)	
Grade 2-3	9 (75%)	7 (20%)	0.001
Cervical stromal involvement	6 (50%)	2 (5.7%)	0.002
>1/2 myometrial invasion	9 (75%)	4 (11.4%)	0.001
≥2cm tumor diameter	9 (75%)	10 (28.5%)	0.04
Mean Ca-125 (IU/mL)	55.5	19.4	0.01
Mean Ca-19.9 (IU/mL)	117.7	21.4	0.01

were mostly multiparous and postmenopausal bleeding was the most common symptom; which were consistent with the literature (Melhem and Tobon, 1987; Jalloul et al., 2012). Mean BMI of patients was 32.4 ± 2.7 kg/m^2; however in Type 2 endometrium cancers like serous and clear, patients are generally not obese. Musa et al.(Musa et al., 2012) found mean BMI of patients 28kg/m^2 for Type 2 ECs.

LVSI is tumor cells' being found within the wall of lymphovascular endothelial cells. LVSI is important for predicting high risk disease in endometrial cancer. Guntupalli et al. (2012) found LVSI as an independent risk factor for nodal metastasis and poor outcomes in endometrioid endometrial cancer. Ayeni et al. (2013) also defined positive LVSI as a significant adverse prognostic factor. Vaizoglu et al. (2013) found LVSI as the sole independent predictor of lymph node metastasis in clinical early stage endometrial cancer and offered routine evaluation of LVSI during frozen section analysis to decide on lymphadenectomy.

Lymphadenectomy in endometrial cancer detects the extent of disease, specify the patients needing postoperative adjuvant treatment and excise the lymphatic disease. Additionally Musa et al. (2012) found mucinous histology as an independent predictor of lymph node metastasis in multivariate analysis. There is also a direct correlation with poor survival outcomes and nodal metastasis. Thus identifying predictors of LVSI may also help gynecological oncologists during surgery for deciding lymphadenectomy (Vaizoglu et al., 2013). Creasman et al. (1987) reported an increased overall incidence of lymph node metastasis in clinically uterine restricted disease for grade 2 and 3 tumors. Moreover pelvic lymph node metastasis risk is less than 5% in grade 1-2 tumors if the myometrial invasion is less than 50%; however it is approximately 15% in grade 1-2 tumors if the myometrial invasion is higher than 50% (Creasman et al., 1987). Myometrial invasion is an important predictor of lymph node metastasis (Cetinkaya et al., 2014). Patients have a low risk for nodal metastasis when the tumor size is ≤ 2cm, myometrial invasion is ≤1/2 and grade 1 histology is present. In that situation lymphadenectomy should be omitted (Mariani et al., 2010). On the other hand performing lymphadenectomy unnecessarily might increase the morbidity.

We found larger tumor size (≥2cm), elevated Ca125, Ca-19.9 levels, >1/2 myometrial invasion, cervical stromal involvement and higher grade (2-3) significant for the prediction of LVSI in ECs with a mucinous carcinomatous component. Schink et al. (1987) evaluated tumor size as a prognostic factor and they found tumor size as an independent predictor of lymph node metastasis. Moreover they stated the incidence of positive lymph node metastasis risk 5.7% for tumors less than or equal to 2cm. However the risk of nodal involvement is 21.7-40% if the tumor is greater than 2cm. Chung et al. (2006) reported elevated Ca125 values as correlated with advanced stage disease, lymph node metastasis, increased myometrial invasion and positive peritoneal cytology. Additionally they found elevated Ca125 levels as the most important finding for the prediction of lymph node metastasis in

multivariate analysis. Ebina et al. (2002) found elevated serum Ca125 levels and nuclear grade as important predictors of paraaortic lymph node metastasis. Ca19-9 levels are generally elevated in mucinous pathologies nevertheless predicting the malignant potential through Ca19-9 values is limited (Kelly et al., 2010). The degree of myometrial invasion and a positive cervical stromal invasion could upstage an endometrial carcinoma thus they are crucial findings of a pathology report. Sanjuan et al. (2006) found the sensitivity and specificity of evaluating myometrial invasion in intraoperative frozen analysis as 74% and 95% respectively. Larson et al. (1996) found more than 50% myometrial invasion on frozen section analysis as a marker of increased risk for extrauterine disease and lymph node metastasis. Cervical invasion is commonly seen within poorly differentiated tumors if myometrial invasion deeply presents (Morrow et al., 1991). Radical hysterectomy and lymphadenectomy improves survival in endometrial carcinoma patients with cervical stromal involvement (Mariani et al., 2001) because cervical invasion causes a local dissemination through lymphatic pathway and makes it easier to have an extra uterine disease.

Grade of the disease shows the aggressiveness of tumor cells. High grade endometrial cancers independent from histologic type tend to have a lymphatic dissemination (Ayeni et al., 2013). In logistic regression analysis we found higher grade (2-3) as the independent predictor of LVSI.

Mucinous type endometrial cancers are rare group of tumors however the biologic behaviour in regard to the histologic type is in debate. Nevertheless preoperative and intraoperative risk factors and findings may indicate the aggressiveness of tumor during surgery. Positive LVSI is a poor prognostic factor and is in association with lymphatic dissemination. Thus preoperative elevated Ca125, Ca-19.9 levels in combination with tumor diameter, myometrial invasion and cervical stromal involvement might show the patients with an increased risk of positive LVSI. Especially grade of tumor is a crucial factor in determining LVSI.

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