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Prognostic significance of Matrix Metalloproteinases 2 and 9 in Endometrial Cancer

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A B S T R A C T

We investigated the prognostic significance of matrix metalloproteinases 2 (MMP 2) and 9 (MMP 9) in endometrial cancer (EC). The expression of MMP 2 and MMP 9 was analyzed immunohistochemically in 73 primary EC patients. In most cases, the gelatinases were predominantly localized to epithelial cell of tumor origin. In univariate analysis histological type, tumor grade, FIGO (1988) surgical stage and high stromal MMP 2 expression were identified as a significant determinant for EC recurrence, while epithelial MMP 2 expression and epithelial and stromal MMP 9 expression were not. Multivariate analysis revealed a subgroup of patient age ≥63.6 years with endometrioid adenocarcinoma and papillary serous carcinoma, all FIGO (2009) stage I disease where strong staining of stromal MMP 2 increase risk of EC recurrence (p=0.037).

***Key words**: matrix metalloproteinase 2, matrix metalloproteinase 9, endometrial cancer, recurrence*

Introduction

Endometrial cancer (EC) is the most common gynecologic malignancy in the United States. Worldwide each year 142,000 women are diagnosed, and 42,000 women die from this disease[1]. Many clinical and pathologic factors influence the likelihood of EC recurrence and survival: surgical stage, patient age, histological type, tumor grade, depth of myometrial invasion, lymphovascular space invasion (LVI), lymph-node involvement, tumor size, expression of estrogen receptors (ER) and expression of progesterone receptors (PR)[1–3]. FIGO surgical stage is the most important overriding variable because it incorporates many of the most important prognostic factors. The revised 2009 FIGO staging system had a higher prognostic value than the 1988 FIGO staging system[4]. However, even for the patients in the same stage the clinical courses are highly variable[2]. Although well-documented prognostic factors are reliable in general, better markers to predict the outcome of an individual tumor are needed.

Experimental studies have reported a correlation between matrix metalloproteinases (MMPs) expression and the invasive potential of malignant tumors[5]. MMPs are a family of enzymes, consisting of 28 members, responsible for degradation of the extracellular matrix (ECM) components in normal embryogenesis and remodeling and in many disease processes such as arthritis, cancer, periodontitis and osteoporosis[6–8]. Tumor invasion and metastasis are exceedingly complex processes that includes tumor growth, local proteolysis and migration of the tumor cells through the degraded tissue[9]. Local proteolysis is carried out by proteinases produced by the tumor cells or by the surrounding stromal cells. MMPs are capable of degrading essentially all macromolecules of the ECM[10]. Many studies have shown the involvement of MMPs in

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physiological and pathological processes in the endometrium[5,11–13]. Key effectors in matrix remodelling of normal endometrium throughout the menstrual cycle are MMPs and tissue inhibitors of metalloproteinases[11,12]. A number of molecular genetic studies employing knock-out or transgenic animals and tumor cell lines, modified to overexpress or down regulate a specific MMP, have demonstrated a correlation between MMP expression and the invasive potential of malignant tumors[5]. Amongst many MMPs that have been identified, MMP 2 (Gelatinase A) and MMP 9 (Gelatinase B) have been hypothesized to be key enzymes, as they degrade type IV collagen, the main component of ECM[11,14].

No conclusive data exist concerning the role of gelatinases as a prognostic factors of EC. Therefore, the aim of this study was to assess the significance of epithelial and stromal MMP 2 and MMP 9 expression in EC in predicting the EC recurrence after definitive surgery for endometrial cancer.

Patients and Methods

The current study utilized tissue from 73 patients undergoing surgery for endometrial carcinoma at the University Hospital Centre Sestre Milosrdnice – University Hospital for Tumors, Zagreb, Croatia and University Hospital Centre Split, Croatia, in the period from 1999 to 2008. At each hospital, the Human Ethics Committee approved the research project and informed consent was obtained from each patient. Formalin-fixed and paraffin-embedded tumor samples were immunohistochemically analyzed for the gelatinases. All tissues were examined by specialist pathologist. The median age of patients was 66 years (range, 38–86). The new FIGO classification of endometrial cancer was introduced 2009, and all our patients underwent surgery before, so they were classified based on 1988 FIGO staging system. 50 patients were with stage I, 5 were with stage II, 16 were with stage III and 2 were with stage IV. Histological diagnoses were endometrioid adenocarcinoma (EAC) in 46 patients, papillary serous carcinoma (PSC) in 20 patients and clear cell carcinoma (CCC) in 7 patients. Tumors were graded histologically according to the International Federation of Gynecology and Obstetrics[15], 24 were grade I (G1), 25 were grade II (G2) and 24 were grade III (G3).

This retrospective study was based on clinical, histopathological and immunohistochemical data. We assessed the prognostic significance of patient age, histological type, tumor grade, FIGO surgical stage and epithelial and stromal MMP 2 and MMP 9 expression in EC.

Immunohistochemical analysis

Immunohistochemical staining of epithelial and stromal MMP 2 and MMP 9 expression was performed using an automated system (Dako Autostainer). Formalin-fixed tissues were embedded in paraffin wax and cut at 2–3 μm thickness. Sections were deparaffinized in histosol and rehydrated in a graded series of ethanol. Water bath antigen retrieval is performed for 20 minutes at 96 °C, at pH 6.10, using Target Retrieval Solution (Dako, Denmark). Endogenous peroxidase activity was eliminated by incubating the slides in 3% hydrogen peroxide for 10 minutes at room temperature. Polyclonal Rabbit Anti-Human MMP 2 (Cat. No. ab52756, Abcam, USA) at a dilution 1:40, and Polyclonal Rabbit Anti-Human MMP 9 (Cat. No. A0150, Dako, Denmark) at a dilution of 1:50, were used as a primary antibodies. Antibodies were diluted in Dako Antibody Diluent with Background-Reducing Components (code S3022). The total area of immunostained section was analyzed and the percentage of positive immunostaining of cancer cells was estimated visually. The amount of immunostaining-positive cancer cells was regarded as the most important element[16]. A percentage score was defined as follows: Score 0, stained cells less than 10%; score 1, stained cells between 10 and 25%; score 2, stained cells between 25 and 50%, and score 3 more than 50%. Further in the text we use term null for score 0, A for score 1, B for score 2, and C for score 3, for statistical analysis.

Statistical analysis

Data were analyzed using statistical software package R (version 2.12). Chi-squared test (χ^2 test), was used to examine the relation between qualitative variables. Kaplan-Meier survival analysis was used for EC recurrence analyses, Log rank test was used for univariate analysis, Cox regression test and Recursive partitioning were used for multivariate analysis. We set the definition of statistical significance to 0.05 or less. Analyses were carried out using the date of surgery as the starting point, and diagnosis of EC recurrence as the primary endpoint.

Results

A total of 73 patients were included into the analysis. The mean age of patients was 65.2±10.9 years (range, 38 to 86 years). The median follow up time of all patients was 18 months. EC recurrence appeared in 31 (42.5%) of 73 patients. The median time from diagnosis to EC re-

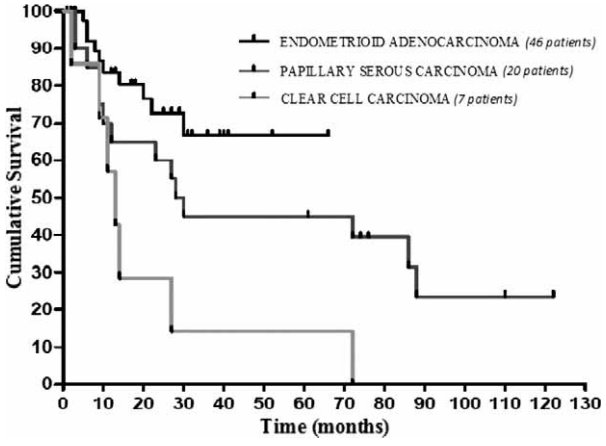

Fig. 1. Kaplan-Meier analysis of disease-free survival for 73 endometrial cancer patients stratified by histological type. Endometrioid adenocarcinoma showed a trend towards better disease-free survival compared to papillary serous carcinoma and clear cell carcinoma (log-rank test, p=0.005).

currence was 72 months. EAC (63%) was most frequent histological type, followed by PSC (27.4%) and CCC (9.6%).

In univariate analysis histological type, tumor grade, FIGO (1988) surgical stage and high stromal MMP 2 expression were identified as a significant determinant, while epithelial MMP 2 expression and epithelial and stromal MMP 9 expression were not. Analysis showed that CCC recurrence is most common and endometrioid adenocarcinoma recurrence is most rarely (log-rank test, p=0.005, Figure 1). 24 (32.9%) of the tumors were grade I (G1), 25 (34.2%) were grade II (G2) and 24 (32.9%) were grade III (G3). Analyses showed an association between higher tumor grade (log-rank test, p<0.001, Figure 2.) and EC recurrence, and FIGO (1988) surgical stage (log--rank test, p<0.001, Figure 3) and EC recurrence. Immunohistochemical staining of epithelial and stromal MMP 2 and MMP 9 expression was performed (Figures 4a-d). In most cases, the gelatinases were predominantly localized to epithelial cell of tumor origin (Tables 1 and 2). Groups null and A were united in a group of low gelatinases expression, and group B and C in a group of high gelatinases expression. We did not found a statistically significant increase in EC recurrence in patients with low or high epithelial MMP 2 expression (log-rank test, p= 0.344) and with low or high epithelial (log-rank test, p=0.220) and stromal (log-rank test, p=0.980) MMP 9

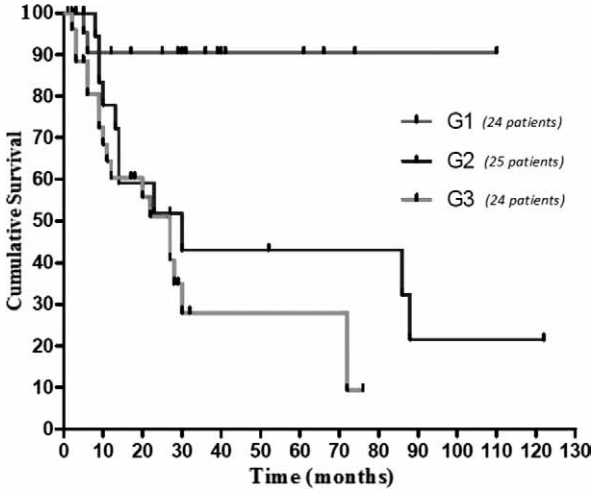

Fig. 2. Kaplan-Meier analysis of disease-free survival for 73 endometrial cancer patients stratified by tumor histological grade. G1 tumors showed a trend towards better disease-free survival compared to G1 and G2 tumors (log-rank test, p<0.001).

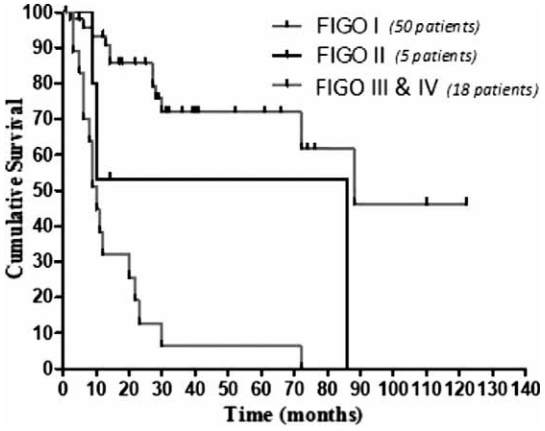

Fig. 3. Kaplan-Meier analysis of disease-free survival for 73 endometrial cancer patients stratified by FIGO (1988) surgical stage. Patients with stage III and IV are in one group, because of only two patients with stage IV. Patients with lower stages of disease showed a trend towards better disease-free survival (log--rank test, p<0.001).

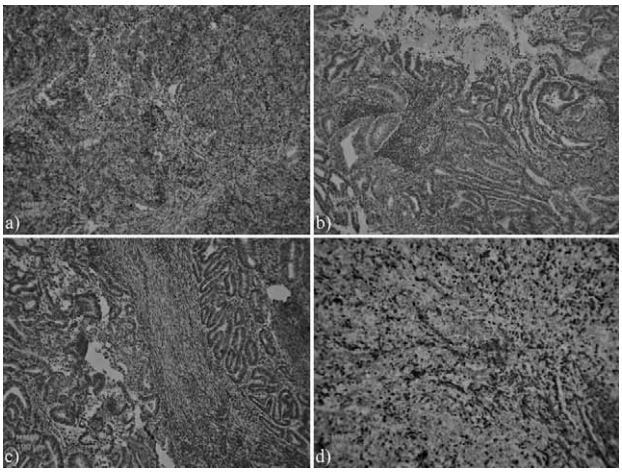

Fig. 4. Immunohistochemical staining of epithelial and stromal matrix metalloproteinases 2 (MMP 2) and 9 (MMP 9) expression a) stromal MMP 2 level C, epithelial MMP 2 level C b) stromal MMP 2 level null, epithelial MMP 2 level C c) stromal MMP 9 level null, epithelial MMP 9 level C d) stromal MMP 9 level C, epithelial MMP 9 level null.

TABLE 1
PRESENTATION OF TUMOR TISSUE AREA RELATED TO MATRIX METALLOPROTEINASE 2 EXPRESSION

Tumor tissue area	Null	A	B	C
Epithelium	25	4	9	35
Stroma	43	8	12	10

Null – stained cells less than 10%, A – stained cells between 10 and 25%, B – stained cells between 25 and 50%, C – more than 50% stained cells

TABLE 2
PRESENTATION OF TUMOR TISSUE AREA RELATED TO MATRIX METALLOPROTEINASE 9 EXPRESSION

Tumor tissue area	Null	A	B	C
Epithelium	31	14	10	18
Stroma	50	6	6	11

Null – stained cells less than 10%, A – stained cells between 10 and 25%, B – stained cells between 25 and 50%, C – more than 50% stained cells

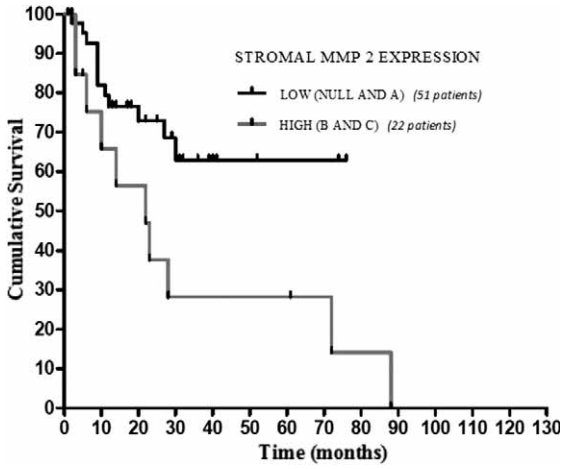

Fig. 5. Kaplan-Meier analysis of disease-free survival for 73 endometrial cancer patients stratified by stromal matrix metalloproteinase 2 (MMP 2) expression. High stromal MMP 2 expression was associated with increased risk of EC recurrence (log--rank test, p=0.020).

expression. High stromal MMP 2 expression was associated with increased risk of EC recurrence (log-rank test, p=0.020, Figure 5).

We used the Recursive partitioning analysis to examine interactions of different prognostic factors. In multivariate analysis we have included only those variables that were statistically significant in univariate analysis. Rpat and Mvpart algorithms revealed several prognostic factors. Rpart algorithm revealed FIGO (1988) surgical stage as major prognostic factor associated with recurrence of disease (log-rank test, p<0.001) that yielded a segment with FIGO Ia, Ib, Ic and IIa (relative risk of recurrence 0.53, the median time from diagnosis to EC recurrence was 88 months) and a segment with FIGO IIb, IIIa, IIIc, IVa (relative risk of recurrence 2.97, the median time from diagnosis to EC recurrence was 10 months). The same procedure continued following this splitting algorithm. In the left segment (FIGO Ia, Ib, Ic and IIa), tumor histological grade appeared to be the strongest prognostic factor which yielded a subgroup of G1 (relative risk of recurrence 0.16) and a subgroup of G2 and G3 (relative risk of recurrence 0.84) (log-rank test, p= 0.012). The median time from diagnosis to EC recurrence of patients with G1 tumor could not be assessed because the majority of patients who were followed did not experience an EC recurrence. In patients with G2 and G3 tumors the median time from diagnosis to EC recurrence was 72 months. Mvpart algorithm corroborated FIGO (1988) surgical stage as major prognostic factor associated with recurrence of disease (log-rank test, p< 0.001). The node with FIGO Ia, Ib, Ic and IIa (relative risk of recurrence 0.53) could be split into a subgroup with EAC and PSC (relative risk of recurrence 0.37) and subgroup with CCC (relative risk of recurrence 2.03) (log-rank test, p<0.001). The median time from diagnosis to EC recurrence of patients with EAC and PSC was 88 months, and in patients with CCC was 14 months. The node with FIGO Ia, Ib, Ic and IIa and with EAC and PSC could be split into a subgroup with age <57.5 years (relative risk of recurrence 0.13) and subgroup with age ≥57.5 years (relative risk of recurrence 0.51) (log-rank test, p<0.001). The node with FIGO Ia, Ib, Ic and IIa and with EAC and PSC and with age ≥57.5 years could be split into a subgroup with age <63.5 years (relative risk of recurrence 1.69) and subgroup with age ≥63.5 years (relative risk of recurrence 0.32) (log-rank test, p=0.002). The node with FIGO Ia, Ib, Ic and IIa and with EAC and PSC and with age ≥63.5 years could be split into a subgroup with low (null and A) stromal MMP 2 expression (relative risk of recurrence 0.11) and a subgroup with high (B and C) stromal MMP 2 expression (relative risk of recurrence 1.16) (log-rank test, p=0.037). These results were statistically significant.

Discussion

Studies regarding EC have shown the presence of multiple factors, which affect prognosis for all stages of the disease. These can be listed as patient age, surgical stage, tumor grade, histological type, myometrial invasion, LVI, lymph-node involvement, tumor size, cervical invasion, expression of ER and PR[1–3,17]. MMPs have long been associated with malignancy, their role in EC and other gynecological malignancies has not been clearly established[18]. ECM-degrading enzymes (including MMP 2 and MMP 9) have been given considerable attention for their roles in invasion and metastasis in malignant neoplasms[19]. Gelatinases are prognostic factors in many adeno- and epithelial cancers[16]. MMP 9 may be considered as a viable biomarker that can be used together with other prognostic factors such as vessel invasion and pT stage to predict the prognosis of patients with completely resected pathologic stage Ia non-small cell lung cancer[20]. MMP 2 and MMP 9 are involved in the invasion process of oral cancer, and MMP 9 is related to poor prognosis in the subset of patients without neck node metastasis[21]. Prognostic value of gelatinases expression in EC is controversial. A few studies have shown a correlation between MMP 2 and/or MMP 9 expression and the histological grade and disease stage of EC[16,22,23]. Both gelatinases correlate to the histological grade of EC. MMP 9 correlates to the clinical stage of the disease[16]. There is no association with either depth of invasion, menopausal status, or the age of the patient[16]. Inoue at al[16,24] found no correlation between the disease outcome and MMP 9 in EC, and in Moser's work[25] MMP 2 was not associated with overall survival. Aglund et al.[16] found substantial influence of MMP 2 and MMP 9 in the clinical behavior of EC. Increasing expression of MMPs and EC progression are closely related[22]. Active gelatinases are present in EC, resulting in alterations to the microenvironment that promote tumor invasion and metastasis[22]. Both gelatinases seem to have influence in the clinical behavior of EC[16]. MMP 2 overexpression is also related to the infiltrative nature of endometriotic lesions in endometriosis[23].

In our study histological type, tumor grade, FIGO surgical stage and high stromal MMP 2 expression are shown to have a statistically significant influence on EC recurrence in the univariate analysis. Rpart and Mvpart algorithm revealed FIGO (1988) surgical stage as major prognostic factor associated with EC recurrence. Rpart algorithm revealed tumor grade as second prognostic factor associated with EC recurrence in lower stages of disease (FIGO Ia, Ib, Ic and IIa). Mvpart algorithm revealed histological type as second prognostic factor associated with EC recurrence in lower stages of disease (FIGO Ia, Ib, Ic and IIa); patient age as a third/fourth prognostic factor in lower stages of disease (FIGO Ia, Ib, Ic and IIa) and in a subgroup of patients with EAC and PSC; finally stromal MMP 2 expression as a fifth prognostic factor in lower stages of disease (FIGO Ia, Ib, Ic and IIa) in subgroup of patients with EAC and PSC and age ≥63.5 years. FIGO (1988) surgical stages (IIb, IIIa, IIIc, IVa) and CCC have been associated with increased risk of EC recurrence. All these results were statistically significant. Rpart and Mvpart algorithm grouped FIGO (1988) stage IIa and FIGO (1988) stage I into one prognostic group. New FIGO (2009) did the same, it classified cervical stromal tumor invasion as stage II and cervical glandular involvement as stage Ia or Ib, depending on myometrial invasion[26], so in conclusion we will update our data to FIGO 2009 criteria.

Univariate and multivariate analysis revealed prognostic significance of high stromal MMP 2 expression in EC recurrence. Results of this study also suggest nonlinear relationship between patient age and disease recurrence.

Conclusion

Results of the present study corroborated FIGO surgical stage as major prognostic factor associated with EC recurrence and confirmed the prognostic significance of the histological type, tumor grade and patient age. We also found an association between EC recurrence and MMP 2. Our study revealed a subgroup of patient age ≥63.6 years with EAC and PSC, FIGO (2009) surgical stage I disease where strong staining of stromal MMP 2 increase risk of EC recurrence ($p=0.037$). FIGO surgical stage, histological type and patient age have influence on prognostic value of MMP 2. According to AJCC (American Joint Committee on Cancer) MMP do not meet the criteria for prognostic factor. Prognostic value of gelatinases expression in endometrial carcinoma is controversial and further studies are needed to assess their prognostic value. Gelatinases might serve as a valuable additional tool for prognostical assessment in EC.

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PROGNOSTIČKA VRIJEDNOST MATRIKS METALOPROTEINAZA 2 I 9 KOD KARCINOMA ENDOMETRIJA

S A Ž E T A K

Istraživali smo prognostičku vrijednost matriks metaloproteinaza 2 (MMP 2) i 9 (MMP 9) kod karcinoma endometrija (KE). Ekspresija MMP 2 i MMP 9 analizirana je imunohistokemijskim metodama kod 73 pacijentice oboljele od KE. U većini je slučajeva ekspresija gelatinaza dominantno izražena u epitelnim tumorskim stanicama. Univarijantna analiza odredila je histološki tip, gradus tumora, FIGO (1988) stadij bolesti i jaku ekspresiju MMP 2 u stromi kao značajne čimbenike u recidivu KE, dok jaka ekspresija MMP 2 u epitelnim tumorskim stanicama i jaka ekspresija MMP 9 u stromi i epitelnim tumorskim stanicama nisu imali utjecaj na pojavnost recidiva KE. Multivarijantna analiza izdvojila je podskupinu pacijentica starosti ≥63,6 godina oboljelih od endometrioidnog adenokarcinoma i papilarnog seroznog karcinoma endometrija FIGO (2009) I stadija bolesti u kojoj je jaka ekspresija MMP 2 u stromi povezana s povećanim rizikom recidiva KE ($p=0,037$).