Prognostic Impact of Urokinase-type Plasminogen Activator and Its Inhibitor PAI-1 in Completely Resected Gastric Cancer

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ABSTRACT

The prognostic impact of the proteolytic factors urokinase-type plasminogen activator (uPA) and plasminogen activator inhibitor type 1 (PAI-1) was evaluated in 76 completely resected gastric cancer patients enrolled in a prospective study. All patients underwent macroscopically and microscopically residual tumor-free resection (category R0, Union International Contre Cancer, 1987). uPA and PAI-1 levels were quantified in detergent-extracted (Triton X-100) specimens of primary gastric tumors by enzyme-linked immunosorbent assays. Median values of 1.57 ng uPA/mg protein were determined in tumor tissue extracts compared to 0.14 ng uPA/mg protein in normal mucosa. For PAI-1, 0.93 ng PAI-1/mg protein was calculated. uPA levels in tumor tissue extracts were significantly correlated with vascular invasion, Lauren classification, and WHO classification, whereas PAI-1 levels showed a significant correlation with advanced lymph node involvement, depth of invasion, tumor stage, site of tumor, and the Lauren, Borrmann, and WHO classifications.

Elevated uPA and PAI-1 levels were found to be associated with poor prognosis. The optimal cutoff values indicating a group of patients with shorter survival were 1.5 ng uPA/mg protein and 1.25 ng PAI-1/mg protein, respectively. Patients with either high uPA or PAI-1 values were significantly associated with decreased survival (median time of survival was 23 months (high) versus 44 months (low)). By univariate Cox regression analysis, it was shown that TNM categories, WHO classification, size of tumor, uPA and PAI-1 levels were all significantly associated with survival. However, in multivariate Cox regression analysis of these grouped variables, nodal status, PAI-1 levels, and WHO classification were the only independent prognostic factors. The relative risks of failure were 5.2, 2.9, and 2.4-fold, respectively. We conclude that PAI-1 and uPA positivity may serve as new prognostic factors in gastric cancer, predicting shorter survival even in clinically important subgroups of patients.

INTRODUCTION

Tumor-associated proteases (e.g., plasmin, uPA, cathepsins, and metalloproteases) and their inhibitors are important factors involved in tumor invasion and metastasis (1–6). In breast cancer, proteolytic factors such as cathepsin D, uPA, and its inhibitor PAI-1 have been claimed to be of independent prognostic value for disease-free and overall survival in several independent studies (7–13). In gastrointestinal cancer, elevated uPA and PAI-1 levels in the primary tumor have been described for esophageal cancer (14, 15), gastric cancer (15–20), and colorectal cancer (18, 21–24) when compared with normal mucosa. For gastric cancer patients, positive correlations of histomorphological data with uPA and PAI-1 levels have been described (17, 19), but to our knowledge the clinical significance of these findings for survival has not yet been demonstrated. We report on a prospective study describing the independent prognostic impact of both uPA and PAI-1 for survival in patients with gastric cancer who have been resected without any indication of residual tumor (category R0, UICC, 1987).

MATERIALS AND METHODS

Patients. Seventy-six patients with gastric cancer (28 women: median age, 63; range, 34–83 years; and 48 men: median age, 64; range, 31–79 years) were consecutively enrolled into a prospective study between April 1987 and December 1989. Inclusion criteria for patients studied were absence of distant or peritoneal metastases and a macroscopically complete and histologically complete surgical removal of the primary gastric cancer (category R0, UICC, 1987; Ref. 25), survival time > 90 days, and a complete follow-up.

Operation. Surgery was performed at the Department of Surgery, Klinikum rechts der Isar, Technical University of Munich. Gastric resection and lymphadenectomy were carried out according to the standardized protocol of the German Gastric Cancer Study Group (26, 27). The lymph nodes of compartments I and II (28) were completely removed by "en bloc" dissection. As a matter of routine, the lymph nodes of the ligamentum hepatoduodenale (station 12) and the retrodudenal lymph nodes (station 13) of compartment III were dissected in patients with advanced cancer (pT > 1) (29). In 35 patients (46%), the tumor was located in the proximal third of the stomach. Nine of these patients were resected by total gastrectomy, 15 by transhiatal or left regional extended gastrectomy, 7 by transmediastinal esophago-fundectomy, and 4 by esophago-gastrectomy. In 12 patients (16%), cancer was located in the middle third, and in 22 patients (29%), in the distal third of the stomach. Twenty-three of these patients were resected by total gastrectomy, 2 by left regional extended gastrectomy, and 9 by subtotal gastric resection. In 7 patients (9%), the entire stomach was affected by carcinoma. Five of these patients were resected by total gastrectomy and 2 by left regional extended gastrectomy.

Histomorphological Examination. The examination followed the protocol of the German Gastric Cancer Study Group (26). Twenty-three patients (30%) were classified as stage I (IA, n = 6, 8%; IB, n = 17, 22%), 13 patients (17%) were classified as stage II, 28 patients (37%) were classified as stage III (IIA, n = 18, 13%; IIIB, n = 10, 13%), and 12 patients (16%) were classified as stage IV. Several histomorphological parameters with prognostic relevance were investigated: exclusion of residual tumor at the resection margins of primary tumor and of the "en bloc" lymph node resectum (category R, UICC, 1987); Borrmann classification (30); diameter and site of tumor; typing and grading according to the WHO classification (31); Lauren classification (32); presence of lymphangiosis carcinomatosa; vascular invasion; and perineural carcinosis. The number of involved lymph nodes, the percentage of involved lymph nodes, and involvement of lymph node compartments I, II, and III (stations 12 and 13, according to the Japanese Research Society of Gastric Cancer; Ref. 28) were investigated in the adherent lymph drainage tissue. For survival analysis, the WHO classification was categorized into "differentiated" and "undifferentiated" type according to the report by Sugano et al. (33).

Follow-up. Adjunct chemotherapy was not administered. Thirty-eight patients (50%) died because of tumor recurrence; the median time of survival of these patients was 20 months (range, 4–51 months). At the end of the observation period, 32 patients (42%) were still alive; their median follow-up was 30 months (range, 19–52 months). One living patient showed a local relapse. Six patients (8%) died due to other causes (four of cardiovascular
disease, one of iatrogenic complication, and one of nephrotic syndrome). For survival analysis, however, these patients were treated as censored observations. The median survival time (34) calculated for all patients was 37 months.

Tissue Extraction and ELISA for uPA and PAI-1. Immediately after resection, fresh tumor specimens and normal mucosa (both about 1 cm²) were selected, snap-frozen, and stored in liquid nitrogen. Cryostat sections (5-μm thickness) were prepared from the tumor specimens and the normal mucosa, which were then stained with hematoxylin and eosin to confirm presence (tumor) or absence (normal mucosa) of tumor cells. Subsequently, 20 to 30 sections of 60 μm each (total wet tissue weight between 70 and 100 mg) were cut for tissue extraction. The last section (5-μm thickness) was also stained by hematoxylin and eosin to demonstrate presence or absence of tumor cells. The still frozen cryostat sections were dipped into liquid nitrogen and then pulverized in a Micro-Dismembrator from Braun-Melsungen (Melsungen, Germany). The still frozen powder was dispersed with 400 μl TBS (0.02 M Tris-HCl-0.125 M NaCl, pH 8.5) containing 1% nonionic detergent Triton X-100 (Sigma, Munich, Germany). The suspension was gently shaken over night at 4°C and then subjected to ultracentrifugation (100,000 × g for 45 min at 4°C) to separate tissue debris. Supernatants were collected, divided into 50-μl aliquots, and stored in liquid nitrogen until use. Levels of uPA and its inhibitor PAI-1 in the tissue extracts were determined by commercially available ELISA kits (American Diagnostica, Inc., Greenwich, CT) for uPA and PAI-1. Details of the kits are described elsewhere (10, 11, 35). The lower limit of detection is 10 pg/ml for uPA and 40 pg/ml for PAI-1. Levels of uPA and PAI-1 are expressed in ng/mg protein. Protein content of the tissue extracts was determined by the Pierce BCA protein assay kit (Pierce, Rockford, IL; Ref. 36).

Statistics. Statistical analysis was performed using the BMDP software package (BMDP Statistical Software, Inc., Los Angeles, CA; Ref. 37). Differences in uPA or PAI-1 levels and histomorphological variables among various groups of patients were analyzed by the Kruskal-Wallis test and the Mann-Whitney two-sample test. All tests were performed at a significance level of P ≤ 0.05. To determine the relative prognostic impact of uPA and PAI-1 compared to established prognostic factors (histomorphological variables) in a prospective fashion, survival was analyzed according to Cox’s proportional hazard model (38). Statistical analyses included continuous as well as binary covariates, all of which were considered as fixed (not time-dependent). For Cox regression, continuous covariates were examined to determine whether the respective failure rate showed an exponential development due to the assumptions of the Cox model. If not, the CART (39–41) technique was used to determine the optimal cutoff value to recode the continuous variable into a binary one. Briefly, CART takes the value with maximal log-rank test for discrimination of high and low levels. The 95% confidence interval for these cutoff points was calculated by a test-based method. Group-oriented curves for survival were calculated according to the Kaplan-Meier (34) model. The relative risks of the various prognostic variables and the corresponding 95% confidence intervals were estimated according to the Cox model.

RESULTS

uPA and PAI-1 Levels in Gastric Cancer and Normal Mucosa.

Cryostat sections prepared from 76 primary tumor specimens of completely resected gastric cancer patients and 15 normal mucosa were extracted by the nonionic detergent Triton X-100, centrifuged, aliquoted, and then analyzed for protein, uPA, and PAI-1 levels. Per tissue block, 20–30 cryostat sections (60-μm thickness; 70–100 mg wet weight) were obtained, yielding ~350 μl extract after centrifugation. The median uPA concentration of the tumor tissue extracts was 5.9 ng/ml (range, 0.38–100 ng/ml), and the median PAI-1 concentration was 4.28 ng/ml (range, 0.04–85.21 ng/ml). The lower limit of detection is 10 pg/ml for uPA and 40 pg/ml for PAI-1. Levels of uPA and PAI-1 are expressed in ng/mg protein. Protein content of the tissue extracts was determined by the Pierce BCA protein assay kit (Pierce, Rockford, IL). The median protein concentration of the tumor tissue extracts was 4.4 mg/ml (range, 1.09–6.52 mg/ml). The uPA and PAI-1 concentration (ng/ml) of each tumor tissue extract was divided by its respective protein concentration (mg/ml), which resulted in uPA and PAI-1 levels expressed in units ng/mg protein. A median value of 1.57 ng/mg protein (range, 0.14–30.2) for uPA and of 0.93 ng/mg protein (range, 0.01–21.2) for PAI-1 was determined (Fig. 2). In normal gastric mucosa, significantly (P < 0.001) lower levels were deter-

Fig. 1. Correlation of uPA and PAI-1 antigen levels determined in tumor tissue extracts by ELISA (ng/ml). Both axes are plotted logarithmically. A weak linear correlation of r = 0.46 between uPA and PAI-1 (P = 0.001) is obtained.

Fig. 2. uPA and PAI-1 levels in extracts of completely resected (R0) gastric cancer tissues (n = 76) compared to extracts of normal mucosa (n = 15). uPA (A) and PAI-1 (B) values were quantified by ELISA. The data are plotted on a logarithmic scale. Horizontal bars, median values. Relationship between characteristics of gastric cancer and uPA and PAI-1 values are presented in Tables 1 and 2.
mined for uPA (0.14 ng/mg protein; range, 0.06–0.35) and for PAI-1 (0.09 ng/mg protein; range, 0.02–0.36). uPA and PAI-1 are not correlated to the extent of inflammation in the specimens investigated.

**Association of Tumor uPA and PAI-1 Levels with Histomorphological Parameters.** Tumor tissue uPA and PAI-1 values were compared to established histomorphological parameters (Tables 1 and 2). In contrast to uPA, PAI-1 level is significantly correlated with tumor invasion, nodal status, metastasis (TNM) and stage. Significantly different values were observed in the following categories: T1 versus T≥2, N0 versus N≥1, M0 versus M≥1, and stage IA versus IB. PAI-1 levels in primary tumor tissue extracts are significantly correlated with advanced lymph node spread (involvement of compartment III, >3 lymph nodes involved, or >20% lymph nodes involved). A lower median level of uPA (1.4 ng/mg protein) was determined in primary tumor extracts of patients without distant lymph node metastases (median value, 2.6 ng uPA/mg protein); the difference approached statistical significance (P = 0.06).

Additional histomorphological data related to uPA and PAI-1 are presented in Table 2. In general, primary gastric tumors that developed in the distal third of the stomach have lower median values of uPA and PAI-1 than tumors arising in other regions of the stomach. Statistically, only the PAI-1 level is significantly elevated in tumors located at the proximal third of the stomach or in tumors covering the entire stomach compared to the distal ones. PAI-1 level but not uPA level is weakly positively correlated (P = 0.94) with tumor size. In three tumors (4%), vascular (venous) invasion was demonstrated. These three cases were significantly associated with a relatively high level of uPA (median value, 7.4 ng uPA/mg protein). If carcinomas are subjected to the Laurén classification, significant lower median values of uPA and PAI-1 were observed for diffuse-type carcinomas than for intestinal-type carcinomas. uPA and PAI-1 are also significantly lower in signet-ring cell carcinomas (WHO classification) than in papillary differentiated and undifferentiated (medullary) carcinomas. In addition, tubulary differentiated carcinomas exhibit significantly lower median values of both uPA and PAI-1 than undifferentiated carcinomas. If tubular differentiated carcinomas are compared to papillary carcinomas, only the median uPA levels are significantly lower than for intestinal-type carcinomas. uPA and PAI-1 are also significantly lower in signet-ring cell carcinomas (WHO classification) than in papillary differentiated and undifferentiated (medullary) carcinomas. In addition, tubulary differentiated carcinomas exhibit significantly lower median values of both uPA and PAI-1 than undifferentiated carcinomas. If tubular differentiated carcinomas are compared to papillary carcinomas, only the median uPA levels are significantly lower. Carcinomas identified macroscopically as a scirrhus-infiltrative growing pattern (Borrmann type IV) are associated with significantly lower PAI-1 values than exophytically growing carcinomas (Borrmann type I). In addition, macroscopically diagnosed early gastric carcinomas contain significantly lower values of uPA and PAI-1 than macroscopically advanced carcinomas. Neither lymphangiosis nor perineural invasion or grading are correlated with uPA or PAI-1.

**Table 1 Correlation of median uPA and PAI-1 levels determined in primary tumors of completely resected (R0) gastric cancer patients (n = 76) with criteria of the UICC staging system (TNM) and lymph node involvement**

<table>
<thead>
<tr>
<th>Stage</th>
<th>uPA (ng/mg protein)</th>
<th>PAI-1 (ng/mg protein)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>0.8 (0.01–2.8)</td>
<td>0.0 (0.01–2.0)</td>
</tr>
<tr>
<td>IB</td>
<td>1.0 (0.01–2.0)</td>
<td>0.0 (0.01–2.0)</td>
</tr>
<tr>
<td>II</td>
<td>1.2 (0.01–2.0)</td>
<td>0.0 (0.01–2.0)</td>
</tr>
<tr>
<td>III</td>
<td>1.4 (0.01–2.0)</td>
<td>0.0 (0.01–2.0)</td>
</tr>
<tr>
<td>IV</td>
<td>1.6 (0.01–2.0)</td>
<td>0.0 (0.01–2.0)</td>
</tr>
</tbody>
</table>

* Kruskal-Wallis group test, P < 0.05; Mann-Whitney two-sample test; n.s., not significant.

* T1/T2, P < 0.01.

* N0/N1, P < 0.01.

* Number according to the Japanese Research Society of Gastric Cancer.

* 0%/>20%, P = 0.01.

* IA/IB–IV, P ≤ 0.01.
levels. No statistically significant difference is seen between protein values and number of tumor cells in the specimens.

**uPA/PAI-1 and Survival Analysis.** To determine whether u-PA and/or PAI-1 levels in primary tumors of completely resected gastric cancer patients, survival was calculated using the Cox proportional hazard model. For this purpose, the observed relative risk of failure was plotted as a function of uPA and PAI-1 levels in primary tumors are of prognostic relevance in completely resected gastric cancer patients, survival was calculated using the Cox proportional hazard model. For this purpose, the observed relative risk of failure was plotted as a function of uPA and PAI-1 levels. Protein (1.5 ng/mg; confidence interval, 1.33—1.73) was determined as the optimal cutoff value for uPA discriminating 37 patients (49%) with uPA <1.5 ng/mg protein and 39 patients (51%) with uPA ≥1.5 ng/mg protein. For PAI-1, a cutoff value of 1.25 ng/mg protein (confidence interval, 1.02—1.99) was determined, discriminating 45 patients (59%) with PAI-1 <1.25 ng/mg protein and 31 patients (41%) with PAI-1 ≥1.25 ng/mg protein. Actuarial survival curves (Kaplan-Meier) illustrate the increased hazard rate of patients with either high uPA or PAI-1 levels (Figs. 4 and 5). The median survival time in each identified group did not significantly differ for uPA and PAI-1: above the cutoff value, 25 (uPA) or 22 (PAI-1) months; and below the cutoff value, 44 (uPA) or 43 (PAI-1) months, respectively. It is worth mentioning that PAI-1 survival curves diverged even further than those for uPA, exhibiting a higher log-rank test value of survival (P = 0.001).

Survival curves (not shown) were also plotted for TNM, stage, and other important morphological variables to determine the prognostic impact of uPA and PAI-1 for survival in important subgroups: T1,2, N1,2, M0, stage III+IV, and both types of WHO classification. The cutoffs for high/low uPA and PAI-1 levels used for the subgroup analysis (Table 3) were those determined for the whole sample. If the N1 and N2 subgroups (15 and 35 patients, respectively) are considered separately, the prognostic impact of PAI-1 for survival remains somewhat below the significance limit (N1, P = 0.089; N2, P = 0.09). If N1 and N2 are lumped together, PAI-1 is significant at the level P = 0.014. PAI-1 fails to be a prognostic discriminator for survival in node-negative patients, T3,4 patients, patients with distant lymph node metastasis, and patients with stage I+II. uPA is not as powerful as PAI-1 in subgroups; it only discriminates for survival in the T1,2, M0,
and WHO-differentiated subgroups. However, PAI-1 discriminates in these subgroups at an even higher level of significance. One should keep in mind that statistical trends for survival in subgroups are more difficult to detect than in the entire collective.

**DISCUSSION**

As yet, no tumor biological prognostic factor for increased mortality has been described in completely (R0, UICC, 1987) resected gastric cancer. We now discuss the clinical relevance of the tumor-associated protease uPA and its inhibitor PAI-1, which are significantly elevated in gastric cancer tissue extracts compared to normal mucosa. Our new finding is that these proteolytic factors may serve as prognostic factors for overall survival in completely resected gastric cancer patients; patients with high uPA or PAI-1 antigen levels in their primary tumors exhibit shorter survival.

For an interpretation of our findings, we are going to discuss our patient population and the results of other studies concerning uPA and PAI-1 in gastric cancer. Our UPA and PAI-1 results were significantly correlated with survival in univariate analysis (cancer cells, Table 4). In contrast, sex, site of tumor, Borrmann classification, Lauren classification, and grading are not associated with survival. To determine the independent value and the RR of the significantly correlated prognostic factors, we used multivariate Cox regression analysis (see Table 5). Three prognostic factors were found to be of independent value: Nodal status, WHO classification, and PAI-1. The RR for death is five times higher in the 50% (66%) lymph node-positive patients than in the 26% node-negative patients (34%). The RR is about three times higher for the 31% patients (41%) with PAI-1 > 1.25 ng/mg protein than for patients with lower PAI-1 levels. WHO classification also exhibits an independent prognostic impact. The RR for death is 2.4 times higher in the 32% patients (42%) with undifferentiated carcinoma than in the 44% patients (58%) with differentiated carcinoma. Although significant in univariate analysis, the prognostic impacts of depth of invasion (T) of the primary tumor, distant lymph node metastasis [M1(Lym)], and uPA levels were no longer significant in this model. Note however that uPA becomes an independent factor when PAI-1 is removed from the Cox model.
various forms of uPA, including the enzymatic inactive precursor pro-uPA, free and complexed forms of the activated, two-chain form of uPA, and (pro)-uPA bound to its receptor uPA-R (10). ELISA tests for uPA and PAI-1 have been used previously in prognosis-related breast cancer studies and were found to be superior to activity assays (9—13).

In our group of completely resected gastric cancer patients, various histomorphological parameters are related to uPA and PAI-1 levels. A significantly lower level of uPA and PAI-1 was observed in signet-ring cell carcinomas, poorly differentiated carcinomas (WHO classification), and diffuse-type carcinomas (Lauren classification). In the same investigation, Takai et al. (17) reported that lower uPA values are associated with incidence of signet-ring cell carcinomas. In the same investigation, Takai et al. demonstrated (in contrast to our results) significantly lower uPA values in poorly differentiated gastric cancer. In another investigation, Nakamura et al. (16) did not find any correlation between uPA or PAI-1 with WHO classification. Our study reveals that the WHO classification suggested by Sugano (33) is itself an independent prognostic factor for survival and that elevated levels of uPA or PAI-1 predict high-risk patients in both WHO subclasses. These findings suggest that biochemical factors, e.g., tumor invasion-associated proteases, are most likely related to the individual biological behavior of a particular cancer rather than to the histomorphological architecture of the tumor.

Gabbert et al. (47) reported tumor-cell dissociation at the invasion front to be an independent prognostic parameter for survival in intestinal-type gastric cancer, significantly associated with vascular and lymphatic invasion. In this respect, tumor cell dissociation was proposed to be one of the first steps in the cascade of tumor invasion (2) and was suspected to be related to down-regulation or malfunction of adhesion-factors, e.g., E-cadherin (48). A second, equally important step is the subsequent degradation of the extracellular matrix by tumor-associated proteases, facilitating tumor spread and metastasis. These findings suggest that biochemical factors, e.g., tumor invasion-associated proteases, are most likely related to the individual biological behavior of a particular cancer rather than to the histomorphological architecture of the tumor.
prognosis (survival). In our group of 76 completely resected gastric cancer patients, multivariate survival analysis (including a variety of prognostic factors determined by univariate analysis) reveals nodal status, PAI-1 levels, and WHO classification (33) to be the only three independent prognostic factors, with relative risks of 5-, 2.9-, and 2.4-fold, respectively.

PAI-1 (10, 13) has already been shown for breast cancer patients to be an independent prognostic factor for both recurrence and survival, even in node-negative patients. Although the observed risk of failure for patients with gastric cancer or for those with breast cancer (10, 12) is similarly correlated with levels of uPA and PAI-1, uPA and PAI-1 cutoffs in the breast cancer study of Jäncke et al. (10) differ from ours, although the very same ELISA tests and method of tissue extraction were used. Cutoffs for uPA and PAI-1 are lower in gastric cancer than in breast cancer: uPA (breast cancer, 2.97; gastric cancer, 1.5 ng/mg protein); and PAI-1 (breast cancer, 2.18; gastric cancer, 1.25 ng/mg protein). This discrepancy could be due to a difference in tumor histology, or it may merely reflect tumor biological features of the different types of cancer. Nevertheless, the prognostic impact (RR) of PAI-1 as determined by multivariate analysis ranged between 2- and 3-fold, both in breast cancer (10) and in gastric cancer specimens (this study).

We attempted to determine the prognostic impact of uPA and PAI-1 in clinically important subgroups of gastric cancer. On the basis of uPA and PAI-1 levels (with cutoffs determined from the sample as a whole), we were able to distinguish patients having worse survival within certain subgroups (T1,2, N1,2, M0, stage III+IV, and WHO classification). Now, a definitive statistical analysis for survival in subgroups will require a larger number of patients. Nevertheless, our data strongly support the conclusion that the tumor-associated protease inhibitor PAI-1, and to a lesser extent uPA, should be considered as new and powerful prognostic factors for survival in completely resected gastric cancer patients.

The prognostic impact of PAI-1 (multivariate analysis) in completely resected gastric cancer is higher than that of uPA. This seems somewhat contradictory, since one would expect high levels of the inhibitor PAI-1 to act protectively by blocking the enzymatic activity of receptor-bound uPA (1–3). However, as pointed out by Jäncke et al. (10) in the context of breast cancer prognosis, high levels of PAI-1 may be of importance for reimplantation of circulating tumor cells at distant loci. Generation and growth of metastases require the formation of a new tumor stroma, which occurs via prevention of uPA-mediated degradation of the extracellular matrix. Moreover, since in normal tissue PAI-1 is present in endothelial cells and platelets, increased PAI-1 levels may reflect a high degree of angiogenesis, thus favoring tumor spread and metastasis. Detailed immunohistochemical and enzymological analysis will therefore be performed to localize uPA and PAI-1 in gastric cancer tissues in order to find out whether uPA concentrations are greatest in tumor cells or in accessory cells at invasive fronts, as well as whether PAI-1 concentrations are highest in main tumor bodies, thereby protecting them from damage by uPA-mediated proteolysis.

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