Significance of Laboratory Studies for Ruling out Metastases in Primary Endometrial Carcinoma

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Abstract. Background: At the time of initial diagnosis of endometrial cancer, therapeutic decisions depend on the recognition of remote metastases. Tumor markers and hepatic enzymes are frequently used to screen for metastases. This study aimed to assess the clinical value of serum concentrations of tumor markers and liver enzymes. Patients and Methods: Laboratory test results from all patients with the initial diagnosis of endometrial cancer treated in our department between 1990 and 2000 were retrospectively reviewed. Hepatic enzyme levels and tumor markers relevant for endometrial cancer were recorded. Analysis of variance and post hoc tests were used to rule out or to confirm systematic differences. Significances were examined by the Mann-Whitney test. Results: A total of 336 women were included in the analysis. Recorded data included serum concentrations of alanine aminotransferase (ALT) \( n=228 \), aspartate aminotransferase (AST) \( n=289 \), gamma-glutamyltransferase (Gamma-GT) \( n=176 \) and alkaline phosphatase (AP) \( n=86 \). The following tumor markers were analysed: carcinoembryonic antigen (CEA) \( n=182 \), squamous cell carcinoma antigen (SCC) \( n=40 \), cancer-associated serum antigen (CASA) \( n=10 \), CA 15-3 \( n=5 \), CA 19-9 \( n=21 \), and CA 125 \( n=28 \). Only CEA serum levels differed significantly between patients with endometrial cancer and hepatic and pulmonary metastases at the time of initial diagnosis and patients without metastases. Conclusion: Our data show that neither the level of the tumor markers CEA, SCC, CA 15-3, CA 125, CA 19-9, CA 72-4 and CASA nor the hepatic enzymes AST, ALT, Gamma-GT and AP in routine evaluation accurately predict the presence of remote metastases.

With an incidence of two per 100,000 women under 40 years of age per year and an incidence of 40-50 per 100,000 women between 50 and 90 years of age per year, endometrial cancer is the most frequent malignant disease of the female reproductive tract (1, 2). Each year, approximately 11,500 women in Germany and approximately 37,000 women in the USA are newly diagnosed with this condition (3). The peak age is between 65 and 70 years, and the mean age is 68 years (2-5). In the USA, 75% of these cancers occur in postmenopausal women (3). Depending on the stage, 5-year survival figures vary between 88.9% (stage Ia) and 17.2% (stage IVb) (6). The reason for the very good stage-independent survival of 76.5% published in the FIGO report (6) is related to the relatively early recognition of endometrial cancer. At the time of diagnosis, 75% of patients with endometrial carcinomas are in stage I. Upon initial diagnosis, stages II and III are equally frequent (10.1% and 11%), whereas stage IV is observed in only 3.7% of patients (5). Unless comorbid conditions dictate otherwise, surgical treatment is considered the treatment of choice up to stage III, provided an R0 resection appears feasible.

In addition to their usefulness for assessing hepatic function, serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyltransferase (gamma-GT) and alkaline phosphatase (AP) are often considered indicators for hepatic metastases. This approach often leads to an extensive imaging workup beyond basic hepatic sonography.

Increased levels of tumor markers typical of endometrial cancer are frequently interpreted as a sign of advanced disease and the presence of remote metastases (7).

Based on data from our department, the value of measuring the afore mentioned serum proteins for ruling out remote metastases was assessed.

Patients and Methods

A total of 336 patients with newly diagnosed endometrial cancer, treated in our department between 1990 and 2000, were included in this analysis. The date of the initial diagnosis, patient age at that time, and the clinical or surgical stage in accordance with the TNM
classification (8) were recorded. All the laboratory analyses were from the time before treatment was begun.

Preoperative posterior-anterior chest roentgenograms had frequently been performed and remote metastases were either ruled out or proven by these roentgenograms plus abdominal ultrasonography. Computed tomography (CT) or magnetic resonance imaging (MRI) of organ systems or body cavities was only conducted if there was any clinical suspicion of or prior diagnostic results suggesting metastases. In individual cases, autopsies provided certainty about the disease stage.

During data entry, special attention was paid to comorbid conditions, particularly in patients with clearly elevated laboratory values and in patients with metastases. These factors were considered in the final analysis.

The serum concentrations were grouped according to tumor stage and the results for various metastatic sites were compared. This approach eliminated the requirement for reference ranges.

Variance analysis was utilized to demonstrate variations of the laboratory results due to analytical technique changes during the study period. Any years characterized by systematic errors were assessed by the post hoc test and excluded.

The probability of error was 5% (p=0.05) for both statistical methods.

Results

Of the 336 women with newly diagnosed endometrial cancer, 67.36% were in stage (p)T1 and 13.95%, 16.32% and 2.08% were in stages T2 to T4, respectively.

At the time of initial diagnoses, remote metastases were demonstrated in 2.07% (n=7) of the patients. The most frequent metastatic site was the liver (1.19%, n=4), followed by the lung and the umbilicus (0.59% each, n=2), as well as the skeletal system (0.3%, n=1).

Hepatic enzyme serum levels. Analysis of variance (one-way Anova) and post hoc tests revealed that in 1998, AST and ALT concentrations were different from other years. Data obtained in 1998 were therefore excluded.

For the final analysis, the liver enzyme levels of patients without hepatic metastases were compared to the respective levels from patients with hepatic metastases broken down by stage.

AST was the most frequently determined enzyme with 260 (77.2%) recordings whereas AP was recorded 86 times (25.52%) and was the least frequently determined enzyme (Table I).

None of the serum levels of AST, ALT, Gamma-GT, or AP were significantly different between patients with and without liver metastases. The same was true for the De-Ritis quotient (AST/ALT ratio) (Table I).

Serum levels of tumor markers. The tumor markers CEA, SCC, CASA, CA 15-3, CA 19-9, CA 125, CA 72-4 and CA 54-9 were recorded for this study. For some of these markers, only occasional measurements were available (Table II).
One patient with liver metastases had a CEA serum level of 2.4 U/l, which was not significantly different from the mean value (2.37 U/l) of the 175 women without metastases ($p=0.329$).

The only significant difference was detected between the CEA serum levels of two patients with liver and pulmonary metastases and patients classified as M0. With respect to the other tumor markers, the Mann-Whitney test did not reveal any significant differences between these two patient populations (Table II).

For the patients with intestinal metastases, three CEA levels and one CA 125 level were available. Table III shows that there were no statistical differences compared to patients whose endometrial cancer did not metastasize.

**Discussion**

With respect to stage distribution and metastatic patterns, the patient population included in this study was comparable to populations described in national and international publications and thus these patients reflected a typical population. Among our patients, 67.36% were in stage T1, 13.95% stage T2, 16.32% stage T3 and 2.08% stage T4. The respective numbers from the Munich Tumor Center (MTC) (9) were 75.2%, 10.1%, 11.0% and 3.7% and from the 24th FIGO Annual Report (6) the figures were 69.61%, 12.7%, 13.34% and 4.35%.

Literature reports on the prevalence of remote metastases at the time of initial diagnosis are scarce. Among our patients, 1.19% had liver metastases, while the MTC reported only 0.2% (10). This apparently large difference may be related to the number of patients included (336 versus 3845) or may simply be a variation. The prevalence of pulmonary metastases of 0.59% in this study and 0.6% from the MTC (10) varied from the respective figure of 1.32% from a retrospective 30-year study in Boston (11, 12).

Preoperative serum levels of AST, ALT, Gamma-GT, and AP are usually ordered by the anesthetists as part of their preoperative routine (13), but they are also frequently utilized to assess the probability of liver metastases. Gamma-GT and AP serum levels have been regarded as the most suitable parameters for indicating hepatic metastases. If both enzymes are within the normal range, the presence of hepatic metastases can be ruled out with a negative predictive value of 90% (14), whereas elevated enzyme levels might indicate the presence of hepatic metastases, with a positive predictive value of 80% (14). It has also been suggested that increased serum AST levels might indicate liver metastases, but for AST and AP, the absolute increase above the normal range was irrelevant (15).

In cases of liver metastases, a tendency for AST to show an earlier and more clearly pronounced increase than ALT serum levels has been reported, which was reflected in the De-Ritis ratio, which could exceed 1 or even 2 (16).
hepatic metastasis is rather indicated by an increase of the AP and Gamma-GT in the serum than by a modified De-Ritis ratio. The De-Ritis ratio is more relevant for hepatocellular carcinomas (17). In these cases, it is clearly increased, especially in the preterminal stage where cytoplasmatic AST is acutely released (18).

In our study, AST and ALT, Gamma-GT, and AP serum levels as well as the De-Ritis ratio did not reveal any differences between patients with and without hepatic metastases. This differs from other publications (14-17) and might be related to the small population size, as the only data available were two Gamma-GT, AST and ALT levels and one AP level in patients with metastases.

Even if the hepatic enzymes are considered helpful for screening for liver metastases, imaging techniques, such as hepatic ultrasonography and CT, are more specific and sensitive. These imaging modalities are clearly superior to laboratory parameters (15, 19). In a previous study (20), we were able to demonstrate that neither CT nor hepatic ultrasonographies are meaningful routine diagnostic techniques for the initial diagnosis of patients with endometrial cancer. It is therefore assumed that laboratory parameters considered to be less diagnostically reliable are even less useful in the search for hepatic metastases.

It is customary to check serum marker levels as part of the workup for endometrial cancer. In cases of endometrial carcinoma, the tumor markers CA 15-3, CA 72-4 and CA 125 have been correlated with the disease stage, the depth of myometrial invasion and the nodal status (7, 21-25). But there have also been reports of false-positive high serum concentrations (25) and lack of correlation between CA 125 serum levels and nodal status (26). CA 15-3, CA 19-9, CA 125 and SCC have also been suggested as markers for a poor prognosis (7, 27) or for recurrent disease (7, 27, 28).

Endometrial cancer cells have been shown to express the tumor marker CEA (29). In the present study three patterns of remote metastases were distinguished. One patient had only hepatic metastases, two patients had hepatic and pulmonary metastases, and three patients had intestinal metastases. Serum CEA levels were obtained in all these cases. A significant difference between CEA levels in patients without and patients with metastases was only observed when both hepatic and pulmonary metastases were present. The mean serum level was ten times higher when the lungs and liver were affected by metastases than in cases where no metastatic disease was evident (p=0.019).

None of the other tumor marker serum levels differed between patients with and without metastases. The number of patients with metastatic disease was comparable to other studies (26), but remains a limiting factor. Therefore, interpretation of our results does require some caution. Variations such as the lack of tumor markers in some malignant tumors (30, 31) on the one hand and expression of tumor markers in benign diseases (such as endometriosis (32)) on the other may have had a marked impact on our analysis.

While elevated CA 125, CA 15-3 and CA 19-9 serum levels can be indicators of a reduced lifespan (14, 27) they should not be used to predict remote metastases because serum levels may already be elevated even by FIGO stage III (33).

Tumor markers do have a role in follow-up after the initial treatment (21, 34), but not as prognostic indicators, for which parameters such as depth of myometrial invasion, vascular invasion, histologic classification and the clinical/surgical stage should be used (1).

**Conclusion**

Our data show that neither the level of the tumor markers CEA, SCC, CA 15-3, CA 125, CA 19-9, CA 72-4 and CASA, nor the hepatic enzymes AST, ALT, Gamma-GT and AP in routine evaluation accurately predict the presence of remote metastases.

**References**


