Prognostic Significance of Pre-treatment Serum C-Reactive Protein Level in Patients with Adenocarcinoma of the Uterine Cervix

BARBARA BODNER-ADLER[1], OLIVER KIMBERGER[2], CORA SCHNEIDINGER[1],
HEINZ KÖLBL[1] and KLAUS BODNER[1]

Departments of [1]General Gynaecology and Gynaecologic Oncology, and
[2]Anaesthesiology, Medical University of Vienna, Vienna, Austria

Abstract. *Aim: To evaluate pre-treatment serum C-reactive protein (CRP) level as a prognostic parameter in patients with adenocarcinoma of the uterine cervix. Materials and Methods: Pre-treatment CRP levels were analyzed to determine potential associations with clinicopathological parameters and to assess prognostic value in 46 patients with sole adenocarcinoma of the uterine cervix. Results: The mean (±SD) pre-treatment serum CRP level was 5.82 (7.21) mg/l. Serum CRP concentration significantly correlated positively with age at diagnosis (p=0.001), lymphovascular space invasion (p=0.0026), recurrent disease (p=0.0001) and International Federation of Gynecology and Obstetrics (FIGO) stage (p=0.0002). In multivariate Cox regression models with age, FIGO stage, histological grade and lymph node status, elevated CRP and cancer antigen 125 levels were associated with shortened survival (p<0.05). Overall 5-year survival rate of patients with pre-treatment serum CRP level <5.0 mg/l was 100% compared to 46.9% for patients with pre-treatment CRP level ≥5.0 mg/l. Conclusion: Serum CRP level can be seen as an additional independent prognostic parameter in patients with the rare histological subtype adenocarcinoma of the uterine cervix.*

Cervical cancer is the third most common cancer in women worldwide, with peak incidence in the 40- to 45-year age group (1). Adenocarcinoma of the uterine cervix is a rare

Correspondence to: Barbara Bodner-Adler, MD, Associate Professor, Department of General Gynaecology and Gynaecologic Oncology, Währinger Gürtel 18-20, 1090 Vienna, Austria. Tel: +43 14040029150, Fax: +43 14040029110, e-mail: Barbara.Bodner-Adler@meduniwien.ac.at

histological subtype, representing up to 20% of cervical carcinoma. International Federation of Gynaecology and Obstetrics (FIGO) stage, histological grade, tumour size, lymphovascular space invasion and lymph node metastasis are major prognostic factors reported in literature (1-3). Nevertheless, additional information guiding the patient's management would be helpful. There is much interest in prognostic factors to permit more accurate patient stratification, that will improve clinical decision-making and may contribute to more rational treatment options. Current guidelines for cervical cancer recommend the same treatment regardless of histological subtype, although lower survival rates were reported for the adenocarcinoma subtype (4). Therefore increasing efforts should focus on prognosticators in adenocarcinoma of the uterine cervix.

C-Reactive protein (CRP) is widely used in clinical routine as the most important acute-phase serum protein for monitoring infection. CRP has also been shown to be elevated in patients with a variety of cancer types and an association with prognosis was found. Several studies have shown that patients with cancer have a higher level of circulating CRP than healthy controls prior to clinical diagnosis (5-8). In addition, an increase in serum CRP has been reported to be associated with poor prognosis in oesophageal, liver, colon and lung cancer (9-12). Elevated serum CRP levels have also been linked to impaired survival in patients with different gynaecological malignancies, including cervical, ovarian and endometrial cancer (13-15). However, only few studies reported on the prognostic role of CRP expression in cervical carcinoma (14, 16), with no data investigating exclusively the histological subtype adenocarcinoma of the uterine cervix.

The aim of the present study was to evaluate whether the pre-treatment serum CRP level might be used as a prognostic parameter in patients with adenocarcinoma of the uterine cervix and to investigate a possible correlation between the serum CRP level and various clinicopathological parameters.

Materials and Methods

A total of 46 patients, suffering from histologically proven adenocarcinoma of the uterine cervix, treated and followed-up over a more than a 10-year period until 2015, at the Department of General Gynaecology and Gynaecologic Oncology, Medical University of Vienna, were enrolled in this retrospective study. Clinical data were obtained by chart review. Patients' charts were reviewed to obtain clinical data about age at diagnosis, histology (mucinous/endometrioid/intestinal adenocarcinoma), FIGO stage, histological grade, lymphovascular space involvement, recurrence of disease, lymph node status, pre-treatment serum CRP, cancer antigen 125 (CA 125) and carcinoembryonic antigen (CEA) levels, and time of death or loss from follow-up. Patients with insufficient data and those with secondary malignancies were excluded from this analysis. The Ethics Committee of Medical University Vienna approved the study protocol before data collection was started (EK no. 1108/2016). All patient records were anonymized and de-identified prior to analysis. Patients were staged retrospectively, according to the FIGO staging system for cervical cancer (17). All patients were treated and followed-up according to the standards of the Institution.

CRP measurements. Patients' blood was obtained before treatment by peripheral venous puncture. CRP levels were measured as a part of clinical routine by a commercially available immuno-tubidimetric test according to the manufacturer's instructions (Roche Diagnostics, Idianapolis, IN, USA) (18). The assay covers a range from 5 to 170 mg/l and an intra-assay variability between 1.64 and 3.34% is claimed by the manufacturer. CRP serum levels of <5.0 mg/l are defined as normal.

Statistical analysis. Values are given as the mean (standard deviation, SD) or median (interquartile range), where appropriate. Correlation between clinicopathological parameters and serum CRP, CA 125 and CEA levels was tested using the Spearman correlation coefficient. The end-point of overall survival was used for analysis. Survival probabilities were calculated by the product limit method of Kaplan and Meier (19). Survival times of patients with no evidence of disease, with stable disease, and patients having died of non-cancer-related events were censored at the last follow-up date. Survival times of patients with cancer-related death and of patients with progressive disease at the time of last follow-up were not censored. Univariate and multivariate Cox regression models for overall survival (OS) were performed, including FIGO stage (FIGO IA *vs.* IB *vs.* II *vs.* III-IV), histologic grade (G1, G2 *vs.* G3), age at diagnosis, lymph node involvement (negative *vs.* positive), lymphovascular space involvement (negative *vs.* positive), recurrent disease and median serum CRP, CA 125 and CEA levels. *p*-Values of less than 0.05 were considered statistically significant. The SPSS system (SPSS Inc., Chicago, IL, USA) was used for these calculations.

Results

Patient characteristics. Patient characteristics, CRP levels and clinicopathological findings are given in Table I. The median age at diagnosis was 51 years (range=24-60 years). The 5-year OS rate was 72% (95% confidence interval=0.582-0.89)

Table I. *Patient characteristics, C-reactive protein (CRP) levels and clinicopathological findings in adenocarcinoma of the uterine cervix.*

Parameter	n	CRP, mean±SD (mg/l)	*p*-Value
Total numer of patients	46	-	-
Age at diagnosis			0.001
≤50 Years	20	2.14±3.39	
>50 Years	26	8.76±8.12	
Histology			0.075
Mucinous	28	5.81±4.69	
Endometrioid	16	6.26±10.59	
Intestinal	2	3.05±3.60	
Tumor stage			0.0002
FIGO I	9	3.38±8.11	
FIGO II	17	8.86±7.18	
FIGO III	7	3.88±2.88	
FIGO IV	3	9.8±3.15	
Histological grade			0.21
G1	15	4.18±6.19	
G2	19	7.39±9.44	
G3	12	5.47±4.56	
Lymphovascular space involvement			0.002
No	26	4.51±7.83	
Yes	20	7.67±6	
Lymph node metastasis			0.58
Negative	30	5.48±7.7	
Positive	16	6.36±6.61	
Recurrent disease			0.0001
No	30	3.07±4.92	
Yes	16	9.68±8.25	

FIGO: International Federation of Gynecology and Obstetrics.

and 16 (35%) patients showed recurrence of disease. Findings regarding surgical, irradiation and adjuvant treatment, recurrence numbers and treatment in cases of recurrence are given in Table II. The status at the last clinical observation revealed 23 patients to be alive with no evidence of disease, five with stable disease, two had progressive disease, 10 had died due to their disease and six had died due to other reasons.

Association between pre-treatment serum CRP concentration and clinicopathological parameters. The mean (±SD) serum CRP level in patients with adenocarcinoma of the uterine cervix was 5.83 (±7.21) mg/l prior to therapy. Serum concentration of CRP correlated significantly positively with age at diagnosis (*p*=0.001), lymphovascular space invasion (*p*=0.0026), recurrent disease (*p*=0.0001) and FIGO stage (*p*=0.0002) (Table I). No significant correlation was found between serum CRP level and histology, lymph node status and histological grade (*p*>0.05).

Univariate survival analysis revealed that advanced FIGO stage (*p*=0.02), age >50 years (*p*=0.03), recurrent disease

Table II. *Treatment and recurrence characteristics of patients with adenocarcinoma of the uterine cervix.*

	No. of cases	%
Surgical treatment		
RHE + PLND	27	59
Conization	9	19
PLND staging	7	15
RHE + BoR + PLND	3	7
Adjuvant therapy		
Yes	24	52
RT	20	43
BR (sole)	2	4
CRT	18	39
CHT	16	35
No therapy	22	48
Recurrent disease and site		
Yes	16	35
Pelvic	6	13
Distant	10	22
No	30	65
Treatment of recurrent disease		
Yes	11	24
Surgery	2	4
RT	4	9
CHT	3	6
Combined RCHT	2	4
No treatment	5	11

RHE: Radical hysterectomy; PLND: pelvic lymph node dissection; BoR: bowel resection; RT: radiotherapy; BR: brachytherapy; CRT: combined external-intracavitary irradiation; CHT: chemotherapy consisting of paclitaxel/carboplatin; RCHT: radiochemotherapy.
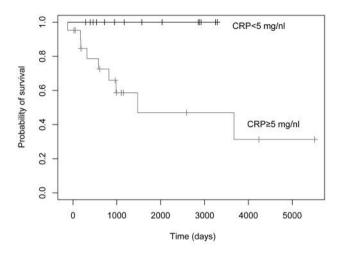

Figure 1. *Kaplan–Meier analysis for overall survival in patients with adenocarcinoma of the uterine cervix, calculated according to serum C-reactive protein (CRP) level.*

(p=0.00015) and elevated serum CRP level (p=0.00038) were associated with impaired OS (Table III). Histology, lymphovascular space involvement, histological grade and lymph node status showed no statistically significant relation to OS (p>0.05).

The 5-year OS rate of patients with a pre-treatment serum CRP level <5.0 mg/l was 100% compared with 46.9% for patients with a pre-treatment CRP level ≥5.0 mg/l (Figure 1). In multivariate Cox regression models with age, FIGO stage, histological grade and lymph node status, an elevated CRP level was significantly associated with shortened survival (p=0.006) (Table III).

Serum CA 125 and CEA levels. The mean (±SD) serum pre-treatment CA 125 level was 108.8 (±149.12) mg/dl and correlated significantly with recurrent disease (p=0.001), higher FIGO stage (p=0.05), higher histological grade (p=0.019) and lymphovascular space involvement (p=0.015). The mean (±SD) serum CEA concentration was 4.534 (±6.65) mg/dl prior to treatment and was significantly associated with higher histological grade (p=0.027),

recurrent disease (p=0.0019) and higher FIGO stage (p=0.04). Moreover, in univariate and multivariate analyses, an elevated serum CA 125 level was significantly associated with impaired overall survival (p=0.02) (Table III).

Discussion

To the best of our knowledge, this is the first report to describe the pre-treatment serum CRP level as an independent prognostic parameter in a subset of patients with histologically proven adenocarcinoma of the uterine cervix. Higher serum CRP levels were found more often in patients with advanced FIGO stage, increased age, lymphovascular space invasion and recurrent disease.

In many types of human cancers, clinical decision-making is based on established clinicopathological prognosticators, which help define the individual patient's risk profile and tailor the patient's therapy accordingly.

For cervical cancer, the current guidelines recommend the same treatment regardless of histological subtype, although several studies reported lower survival rates in patients with the rare adenocarcinoma subtype (4). This might be due to less success in diagnosis and treatment of preinvasive adenocarcinoma compared to squamous cell carcinoma (20). Ongoing efforts have focused on comparing the prognosis of adenocarcinoma to squamous cell carcinoma (21), and there would seem to be a need for additional prognostic markers, especially for the histological subtype adenocarcinoma, in order to define individual patient risk.

Although cervical adenocarcinoma has lower human papillomavirus (HPV) positivity rates than squamous cell

Table III. *Univariate and multivariate survival analysis in patients with adenocarcinoma of the uterine cervix.*

Parameter	Univariate *p*-value	Multivariate HR (95% CI)	Multivariate *p*-value
Serum CRP	0.000381	1.238 (1.064-1.441)	0.00557
Serum CA 125	0.000959	1.012 (1.002-1.022)	0.0175
Serum CEA	0.024	1.3596 (0.950-1.944)	0.0922

CRP: C-Reactive protein; CA 125: cancer antigen 125; CEA: carcinoembryonic antigen; HR: hazard ratio; CI: confidence interval.

carcinoma, the prevalence of HPV infection still ranges from 51-98% (22, 23). Previous reports have discussed inflammation as being a critical part of tumour progression, with various inflammation-induced cytokines playing a role in cervical carcinogenesis, tumour progression and prognosis (24). To date, the prognostic value of serum CRP has been assessed in different human malignancies (25, 26). However, literature regarding the prognostic role of serum CRP in cervical cancer is scanty and mainly focused on squamous cell carcinoma, with no separate data existing for the subset of cervical adenocarcinoma (14, 16). Thus, we aimed to investigate if serum CRP could potentially serve as an additional independent prognostic marker for this histological subtype.

A series of different markers has been investigated for their capability in determining the prognosis in cervical cancer. These comprise the most common and established markers such as squamous cell carcinoma antigen, tissue polypeptide antigen, CEA and CA 12-5 (27, 28). In accordance with previous research, the present study confirmed the prognostic role of CEA and CA 12-5 in cervical adenocarcinoma (14, 27). Additionally, experimental inflammatory markers such as interleukin 1, interleukin 6 and interferon γ were found to be linked with impaired prognosis in cervical cancer (29). The disadvantage of these markers is their limited utility in the daily clinical routine due to the high costs and the need for specially equipped laboratories for their analysis.

In the present study, an elevated pre-treatment serum CRP level was strongly linked with higher FIGO stage, one of the most important prognosticators, indicating that serum CRP could act as a marker of tumour mass and tumour spread in patients with adenocarcinoma of the uterine cervix. Our findings are in line with those of Polterauer and colleagues, who in a large cohort of cervical cancer, mainly representing the squamous cell carcinoma subtype, observed that higher serum CRP levels were significantly associated with advanced tumour stage (14). A similar correlation between CRP and FIGO stage was also detected by Hefler *et al.* in a group of patients with epithelial ovarian cancer (13). Interestingly, in uterine leiomyosarcoma, a rare tumour of smooth muscle origin, the serum CRP level was not significantly associated with the FIGO stage (30).

In fact, high serum CRP could reflect a higher metastatic potential of the tumour, as it is known to promote metastatic spread by various mechanisms, including stimulation of angiogenesis, increase of vascular permeability and acting as an endothelial mitogen (31). This hypothesis fits our observation that higher CRP levels were also detected in patients who demonstrated recurrent disease. This knowledge might possibly be useful in the future for selecting the subgroup of patients who are at higher risk for local recurrence and metastatic spread and who could benefit from additional treatment modalities.

We further analyzed the prognostic value of CRP level prior to therapy with the Kaplan–Meier method and Cox proportional hazards regression. Serum CRP was independently associated with OS. Our data are in line with those of Polterauer and co-workers and support the role of serum CRP as independent prognostic parameter in cervical adenocarcinoma (14). The major advantage of CRP is that it is already a recognized marker of inflammation which is relatively cheap and easy to assay and is generally used in daily clinical routine in laboratories worldwide.

Our results are interesting from the clinical point of view, but we admit that at present, an elevated serum CRP level does not directly influence current treatment strategies and clinical consequences need to be determined. It is unclear if the inflammatory reaction caused by the tumour, and reflected by an increased serum CRP level, can be treated with anti-inflammatory drugs – similarly as in a trial for colorectal cancer (32) – and if this would improve prognosis. Prospective, placebo-controlled randomized trials will be necessary to clarify this issue.

We observed that the pre-treatment serum CRP level was independently associated with prognosis in patients with adenocarcinoma of the uterine cervix, possibly defining a subset of patients with impaired prognosis requiring intense therapy. We are aware of the fact that our results are limited by the relatively small number of cases and the retrospective study design, and further clinical studies with larger numbers of cases need to be performed to establish the prognostic

value of CRP in cervical adenocarcinoma. However, if proven in future studies, serum CRP could potentially serve as a novel, easily available and relatively cheap prognostic marker in cervical adenocarcinoma, helpful in guiding therapy of these patients and define their risk profile.

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