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The Prognostic Value of Nuclear Roundness and Neopterin in Ovarian Cancer

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The prognostic value of clinical factors, morphometric features and neopterin, a marker for macrophage activation, was investigated retrospectively in 68 ovarian carcinoma patients. Nuclear roundness was a good predictor of patient survival. About 50% of our patients showed neopterin concentrations above the cut-off level of 275 μmol/mol creatinine. Interestingly, those patients with elevated urinary neopterin concentration, and thus displaying a sign of activation of cell-mediated immunity, had a shorter survival than those with a normal concentration. Applying a multivariate Cox regression analysis, the only independent parameters predicting patient survival were FIGO stage, residual disease, nuclear roundness and neopterin.
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INTRODUCTION

THE PROGNOSIS for a cancer patient depends in general on three groups of factors. The first includes those variables which characterise the tumour itself. These are tumour stage, grade and histological type [1–3]. More sophisticated methods like the determination of S-fraction, ploidy, oncogenes, tumour-suppressor genes, growth factors or proteolytic enzymes may improve the characterisation of tumours and are more objective [4–10]. The second group of parameters concerns the patient's treatment. Residual disease is a leading prognostic factor in ovarian cancer and is correlated with surgeon's skill [11]. The selected chemotherapeutic regimen, particularly platinum-containing cytostatic drugs, also markedly affects survival of ovarian cancer patients [12]. The last group of prognostic indicators deals with the host. Tumour growth and, therefore, patient survival may also be affected by interactions of the tumour with the immune system, whereby cell-mediated immunity is assumed to influence cancer growth. Macrophages, cytotoxic T-cells and natural killer cells are the effector cells with the potency to reject the growing cancer, like an allogeneic transplant [13, 14].

The subdivision of prognostic factors into these three classes seems reasonable, as each class is mostly independent of the others, e.g. parameters describing the tumour, although often

Table 1. Patients' characteristics

	No. of patients
Total number of patients	68
Median age (range)	62 (29–90)
Histological type	
Serous	41 (60%)
Mucinous	18 (26%)
Others	9 (13%)
FIGO stage	
I	16 (24%)
II	3 (4%)
III	34 (50%)
IV	15 (22%)
Tumour grade	
1	14 (21%)
2	36 (53%)
3	18 (26%)
Mean follow-up (months)	31

related, are independent of those variables describing either the treatment or the host system.

In order to test the described hypothesis, especially the impact of cell-mediated immunity and nuclear morphometry on the prognosis of ovarian carcinoma patients, selected variables from all three groups were included in this study.

PATIENTS AND METHODS

68 women with epithelial ovarian cancer were included in this study (Table 1).

Morphometry

Microscopic fields were selected at random in haematoxylin and eosin-stained 4-μm sections of the primary tumours without subjective choice of 'more malignant' or 'polymorphous' areas, using a pointgrid superimposed on the total section, as recently described [15]. Within each microscopic field, selection of nuclei was guided by the same at random approach, using a pointgrid with nine crosses. Only nuclei with sharp borders and hit by the inner right lower corner of a cross were measured. For each nucleus the mean area (expressed in μm^2) and the nuclear roundness, calculated by division of the minimum nuclear diameter by the maximum nuclear diameter, were determined. An idealised nucleus that is round is rated 1. The more the two axes differ, the lower the nuclear roundness value. Both parameters were selected for their known value as prognostic factors in ovarian cancer and other tumours [16]. At least 15 fields and 60 cells were analysed per case. The focal plane was adjusted individually for every nucleus to achieve sharp demarcations and maximise their projected area. All measurements were performed by means of a CAS-200 system (Becton and Dickinson) regulated by the PRODIT program (Promis, Almere, The Netherlands) and linked via a video camera to a microscope with a 100x high-dry objective (NA = 0.95).

Neopterin

The first morning urine was collected, and protected from light and stored at −20°C until analysed. Using a fully automated high performance liquid chromatography system, neopterin and creatinine were determined simultaneously in the urine specimens, as recently described [17]. Neopterin was quantitated by its native fluorescence (353 mm excitation, 438 nm emission wavelengths). Neopterin concentration was always related to creatinine concentration, which was determined by UV absorption at 235 nm wavelength in the same chromatographic run. Concentrations of both substances were calibrated using external standards.

Interleukin-2 receptor (IL-2R)

In a subset of 28 patients IL-2R was determined either before surgery ($n = 28$) or during follow-up ($n = 13$) in addition to neopterin. The soluble IL-2R (TAC antigen) was measured in serum samples of ovarian carcinoma patients using a comercially available enzyme immunoassay (T Cell Sciences, Cambridge, Massachusetts, U.S.A.).

Statistics

Data were analysed by means of the BMDP statistical software package. Survival of ovarian carcinoma patients was calculated from the time of diagnosis using the product-limit method of Kaplan and Meier. Observed differences in survival were examined according to the generalised Wilcoxon test (Barlow test statistics). Cox proportional hazards analysis was used to identify the independent prognostic factors. Correlations were estimated by the non-parametric Spearman rank correlation coefficient.

RESULTS

Survival analysis of the 68 ovarian carcinoma patients clearly demonstrated the prognostic value of the FIGO staging system (Fig. 1a). Moreover, the size of residual tumour mass left after initial surgery and grading predicted patient outcome (Fig. 1b and c, respectively). These findings are widely accepted and also clearly confirmed in our patient population. Grading, however, may depend on subjective impressions of pathologists. To overcome such an eventual bias, we applied quantitative morphological techniques to characterise nuclear size and shape. Median nuclear area of the 68 patients was 52 μm^2, ranging from 23 to 95 μm^2, and median nuclear roundness was 0.879, ranging from 0.816 to 0.921. Median nuclear area was clearly dependent on grade (Table 2) but not on FIGO stage. Nuclear roundness, on the other hand, was correlated neither to stage nor grade.

Nuclear roundness was a good parameter in predicting patient survival when the patients included in the first quartile were compared with those in the other three (Fig. 2). A subdivision of patients according to the median value or the third quartile did not result in a significant difference. The nuclear area on the other hand, had no impact on the prediction of patient survival (data not shown).

We were able to show increased neopterin levels in ovarian carcinoma patients (Fig. 3). About 50% of our patients showed neopterin concentrations above the cut-off level of 275 μmol/mol creatinine. Neopterin values were correlated neither to FIGO stage nor grade (Table 2).

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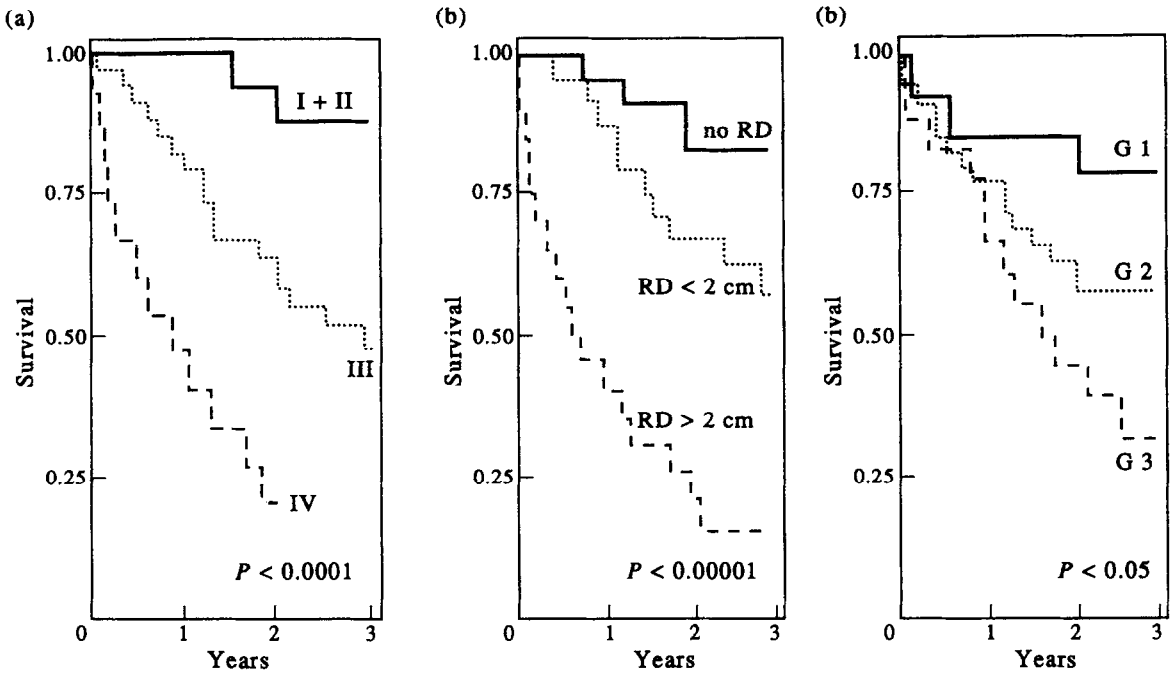

Fig. 1. Survival of ovarian carcinoma patients divided into subclasses based on FIGO stage (a), maximum diameter of residual tumour mass (b) and tumour grade (c). The Kaplan–Meier curves were analysed according to Mantel and Breslow as described in Materials and Methods, and significance levels are indicated.

Neopterin, however, was strongly correlated to the IL-2 receptor, which is another very sensitive marker for activation of cell-mediated immunity, especially for T-cells (Fig. 4). These findings, and those reported by other authors, clearly demonstrate that neopterin is a useful and sensitive marker for the estimation of cell-mediated immunity and that patients may respond to the non-self tumour by activation of effector cells. Interestingly, those patients who showed an elevated concentration of neopterin in their urine had a worse survival rate than those with a normal level ($P < 0.002$, Fig. 5).

In summary, the prognosis of ovarian carcinoma patients from a univariate point of view seems to be dependent on FIGO stage, tumour grade, residual disease, nuclear roundness and neopterin level (Table 3). If a multivariate Cox regression is calculated, then the only independent parameters remaining are FIGO stage, residual disease, nuclear roundness and neopterin.

DISCUSSION

In ovarian cancer, several important prognostic factors have been established. Of these, FIGO stage, residual tumour mass left after initial surgery and tumour grading have been reported [1–3, 11]. This was also confirmed by our study. Tumour grading, however, which depends on the subjective impression of the pathologist, may be replaced by the morphometrically measured nuclear roundness. In contrast to Jan Baak's group, we were unable to demonstrate that the nuclear area has any prognostic value, although this parameter was clearly correlated to grade [18]. One possible explanation could be the difference in selection of measured fields. The group from The Netherlands selected the most atypical areas, this being highly subjective. In agreement with our findings, Mogensen *et al.* did not detect a correlation between mean nuclear profile area and survival [19]. This and our study used routine sections to measure randomly selected nuclei, thus allowing an unbiased estimate of morphometric parameters in ovarian cancer. This method is recommended as it may reduce subjective investigator judgments and improve reproducibility of results.

One important question examined by our study was whether patient survival might also be affected by interactions of the tumour with the immune system. Cell-mediated immunity is assumed to play a major role in influencing cancer growth. To measure cellular immune activation we determined urinary neopterin levels. Neopterin, a low molecular mass substance is biosynthesised from guanosine triphosphate (see [20] for review). It is produced and released in strongly increased quantities by human macrophages upon activation by interferon-gamma [21]. Although its physiological role is largely unknown, it is nevertheless a very sensitive parameter of macrophage activity. For example, in kidney allograft recipients, rejection of the transplanted organ is characterised by a dramatic stimulation of cell-mediated immunity accompanied by a likewise dramatic increase in urinary neopterin [22]. Patients tolerating the new organ have stable and low neopterin excretion. A tumour cell, because of its altered cell surface, may be classified by effector cells as 'non-self' and induce a cascade of immune activation steps. This in turn could result in induced neopterin production. We were able to show increased neopterin levels in about 50% of ovarian carcinoma patients. It is important to mention that neopterin is not a classical tumour marker, because there is no indication that cancer cells themselves excrete it. The only sources of neopterin, to our knowledge, are activated monocytes and macrophages. This may indicate that the immune system recognised the tumour in approximately half of the patients. This was supported by a good correlation of neopterin value with the secreted IL-2R, which indicates T-cell activation, in a subset of patients. It is interesting that patients with elevated neopterin levels, i.e. those with an activated cellular-mediated immunity, were characterised by a shorter survival time. This finding is in agreement with our earlier reports and has also been confirmed in other malignancies [20, 23–25]. Nevertheless, it

Table 2. Morphological parameters and neopterin in patients with ovarian carcinoma

Variable	FIGO stage I+II	III	IV	*P* value*
Nuclear area (μm²)				
Q1	36	45	39	
Median	46	54	47	n.s.
Q3	61	68	65	
Nuclear roundness				
Q1	0.86	0.87	0.86	
Median	0.88	0.89	0.87	n.s.
Q3	0.89	0.90	0.88	
Neopterin (μmol/mol creatinine)				
Q1	185	197	247	
Median	231	258	304	n.s.
Q3	308	457	492	
No. of patients	19	34	15	

Variable	Grade I	I	III	*P* value*
Nuclear area (μm²)				
Q1	33	41	56	
Median	42	50	63	0.001
Q3	50	63	71	
Nuclear roundness				
Q1	0.87	0.86	0.87	
Median	0.88	0.88	0.88	n.s.
Q3	0.89	0.90	0.89	
Neopterin (μmol/mol creatinine)				
Q1	183	188	224	
Median	270	261	291	n.s.
Q3	469	379	490	
No. of patients	14	36	18	

*Levels of statistical significance: patients were grouped according to quartiles of each variable, and the association with FIGO stage or grading was analysed by the Kruskal–Wallis test. n.s., not significant.

deserves comment: from the standpoint of a naive immunosurveillance theory, one would instead expect a beneficial effect of cellular immune activation, as reflected by elevated neopterin concentrations. Three possibilities may explain why the opposite is the case:

— Although increased levels of neopterin and IL-2 receptor demonstrate activation of macrophages and T-cells, we cannot rule out the possibility that some steps of the immune cascade necessary for a reaction against the tumour cells are deficient.

— Another possible explanation is that an elevated neopterin level indicates an insufficient host reaction. This would mean that a highly maligant tumour induces an immune response, but the effector cells are unable to kill their targets. In that case a high neopterin level may be typical of tumours that can survive and grow despite the immune response.

— One valid explanation could also be that activated macrophages produce high amounts of growth factors, for example colony stimulating factors, that can either stimulate tumour proliferation directly or support angiogenesis, which in turn ameliorates tumour nutrition [26].

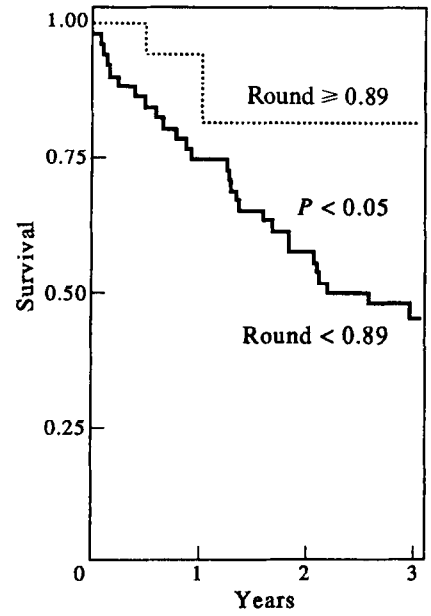

Fig. 2. Survival according to nuclear roundness. Cut-off-point of grouping was the third quartile, resulting in a distribution of 17 patients in the group ≥ 0.89 and 51 patients in the remaining three quartiles.

In the light of these findings, we must also consider the value of so-called immune therapy. As we and others have described, interferon-gamma given intraperitoneally induces remission in about one-third of refractory ovarian cancer patients [27, 28]. All patients, however, respond with an activation of the immune system and a marked increase in serum and urine neopterin. Interferons, therefore, worsen a prognostic factor in ovarian cancer patients. We do not know whether this increased neopterin level is a meaningless phenomenon, or whether it is caused by the same mechanism that is responsible for a bad prognosis.

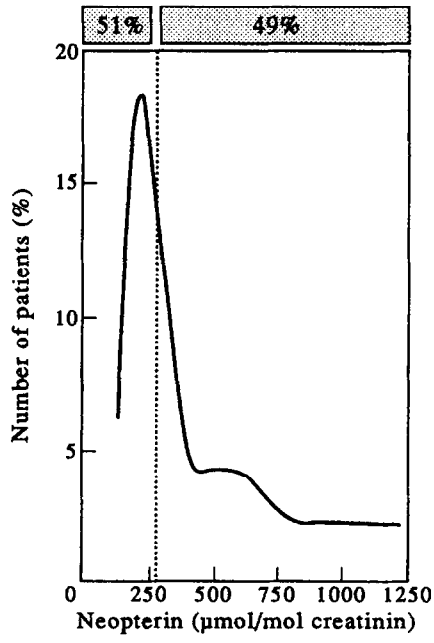

Fig. 3. Distribution of urinary neopterin values in ovarian carcinoma patients.

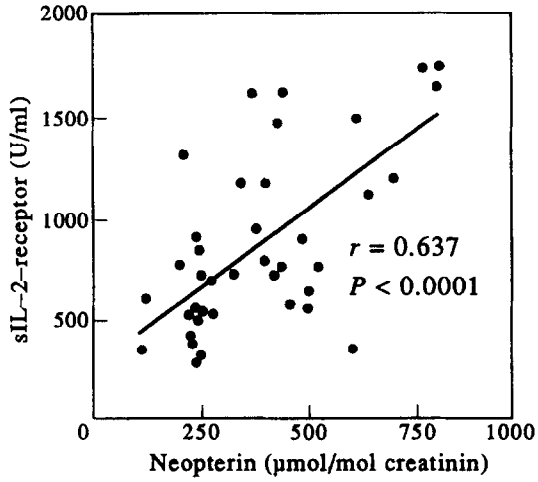

Fig. 4. Correlation of urinary neopterin values with the soluble interleukin-2 receptor (TAC). The measured concentration for each sample was plotted and linear regression calculated. The Spearman rank correlation coefficient is indicated.

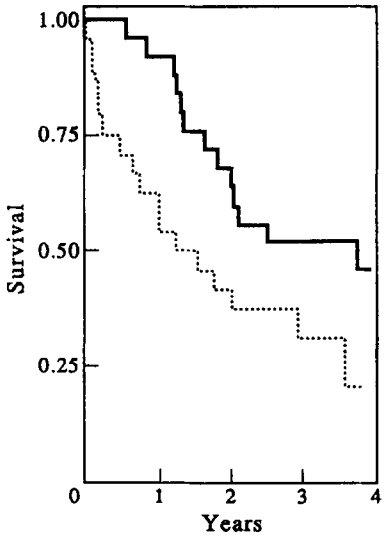

Fig. 5. Survival curves for ovarian carcinoma patients with neopterin levels below (———) and above (----) the cut-off used.

In summary, the findings of our study confirm the hypothesis mentioned in the Introduction, namely that each group of prognostic factors contains at least one independent parameter. Thus it can be stated that tumour characteristics are reflected by FIGO stage and nuclear roundness, therapy by the residual disease, and the host by the neopterin level.

Table 3. Prognostic factors in ovarian cancer

Variable*	Univariate Cox analysis *P* value†	Multivariate Cox regression Regression coefficient Value*	S.E.	*P* value‡	Relative risk§
FIGO stage	0.0003	1.97	0.66	0.0001	4.5
Tumour grade	0.0126	—	—	n.s.	1
Residual disease	0.0012	0.64	0.69	0.0150	1.9
Nuclear roundness	0.0070	−2.59	0.69	0.0001	0.08
Nuclear area	n.s.	—	—	n.s.	1
Neopterin	0.0407	0.73	0.38	0.0481	2.1

*Variables were used in dichotomised form: FIGO stages I and II vs. III and IV; tumour grade I vs. 2 and 3; residual disease none vs. macroscopically visible; nuclear roundness below vs. above 0.894; nuclear area below vs. about 52 μm²; neopterin below vs. about 275 μmol/mol creatinine. †Level of statistical significance at the step 0 (i.e. univariate) for multivariate Cox regression. ‡Level of statistical significance estimated by computing a χ^2 to remove statistic for the respective variable. §Relative risk was estimated as the exponential function of the respective regression coefficient.

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Increasing Survival of Patients with Urinary Bladder Cancer. A Nationwide Study in Sweden 1960–1986

Per-Uno Malmström, Magnus Thörn, Per Lindblad, Reinhold Bergström and Hans-Olov Adami

Survival rates were analysed in 29 055 patients with urinary bladder cancer diagnosed in Sweden from 1960 to 1986 and followed up until 1987. The 2-, 5- and 10-year relative survival rates were 79, 70 and 64% for men and 75, 68 and 63% for women, respectively. Patients with a history of bladder cancer for at least 15 years ran a negligible risk of dying from their disease. Prognosis was consistently better in younger than in older patients; below 50 years of age the 5-year relative survival rate was 90%, as compared with 60% in patients aged 70–79 years. Patients diagnosed between 1960 and 1964 had a 60% 5-year relative survival, as compared to 71% in those diagnosed between 1980 and 1984. Multivariate analyses further confirmed that age but not sex is an important prognostic factor in bladder cancer and, further, that a substantial improvement in survival rates took place during the 1960–1986 period. Compared with 1960–1964 the risk of dying of bladder cancer within 5 years in patients diagnosed between 1980 and 1984 was 51% lower in men [relative risk (RR) = 0.49; 95% confidence interval (C.I.) 0.42–0.57] and 44% lower in women (RR = 0.56; 95% C.I. 0.45–0.70).
Eur J Cancer, Vol. 29A, No. 13, pp. 1868–1872, 1993.

INTRODUCTION

PROGRESS IN treatment of urinary bladder cancer has only been studied to a limited extent. Without treatment, the average survival time from the time of the first symptom has been estimated at 16.5 months [1]. A review of progress in the curability of bladder cancer in the U.S.A. during 1932–1971 revealed only modest improvements [2]. Few population-based analyses of trends in survival are available; and they have usually included relatively small numbers of patients [3–6].

We analysed survival rates with emphasis on temporal trends in nearly 30 000 patients with urinary bladder cancer, diagnosed during 1960–1986, in the total Swedish population. Advantage was taken of the almost complete registration and follow-up procedures available in this country. Relative survival rates were calculated to correct for deaths from causes other than bladder cancer. The possible confounding effect of changing distributions by gender, age at diagnosis and years of follow-up on trends in survival was adjusted for multivariate analyses.

PATIENTS AND METHODS

The Cancer Register

The Swedish National Cancer Register was founded in 1958. All clinicians, pathologists and cytologists must report to the register every patient with a newly diagnosed malignant disease [7]. The Register contains information on gender, date of birth, site or type of cancer, histological classification and date of

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