Shoulder phenomenon:	extension of junctional component over at least three rete ridges beyond the dermal naevocellular component
Abnormal pigment distribution:	retention of melanin throughout dermal naevocellular component
Lymphohistiocytic infiltrate:	0=no; 1=slight, perivascular; 2=moderate, aggregate-like; 3=marked, band-like
Lamellar fibroplasia:	as compared to the papillary dermis in perilesional skin
Neovascularisation:	as compared to the papillary dermis in perilesional skin
Pagetoid cells:	abnormal melanocytes with abundant pale cytoplasma containing dusty melanin

APPENDIX III

The observer agreement for categorical data*

P_o represents the observed proportion of agreement between two observers (the observed proportion of subjects with equal diagnosis for the two observers).

K represents the proportional excess of agreement beyond what is to be expected under independence. The coefficient Kappa is defined by

$$K = \frac{o - e}{1 - e}. \quad (o = \text{observed proportion of agreement}, e = \text{expected proportion of agreement})$$

*Cohen, J. A coefficient of agreement for nominal scales. *Educational and Psychological Measurement* 1960, **20**, 37–46.

Quality of Kappa†

≤ 0.20 Poor/slight
0.21 – 0.40 Fair
0.41 – 0.60 Moderate
0.61 – 0.80 Substantial
0.81 – 0.99 Almost perfect
1.00 Perfect

†Landis J.R. and Koch G.G. The measurement of observer agreement for categorial data. *Biometrics* 1977, **33**, 159–174.

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Lipid-bound Sialic Acid, Prostaglandin E and Histamine in Head and Neck Cancer

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Blood concentration of lipid-bound sialic acid (LBSA), prostaglandin E (PGE) and histamine were determined in 37 patients with carcinoma of hypopharynx and larynx (supraglottic and glottic), in 12 non-cancer patients and in 10 healthy subjects. The concentration of LBSA was significantly increased in 94.4% cancer patients preoperatively and fell to somewhat lower levels within 1 month after tumour resection. In patients with complete tumour resection and no tumour recurrences within 2 years, it steadily decreased thereafter, reaching normal levels within 6–24 months after surgery, whereas in patients with tumour recurrences or incomplete tumour resection it rose again within 6 months after tumour resection. Similarly, the concentration of PGE was significantly increased in about two thirds of cancer patients (67.6%) preoperatively, dropped significantly within 1 month after tumour resection and rose again in patients with tumour recurrences. Preoperative histamine concentration was decreased in 24.3% of cancer patients and postoperatively it rose both in patients with or without tumour recurrences.
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INTRODUCTION

MANY PROGNOSTIC factors have been identified in cancer [1, 2]. Recent investigations have shown that concentrations of serum lipid-bound sialic acid (LBSA) [3–5], blood histamine [6] and serum level or tissue content of prostaglandin E (PGE) [7, 8] can serve as markers for the detection of tumour spread and progression.

Increased serum LBSA [5, 9] and PGE plasma [10] levels have been observed in head and neck carcinoma and both have been reported to correlate with the presence of the disease. Blood

Table 1. Clinical profile of cancer patients in study

No. of patients	Stage/site	Prior therapy	Recurrence	Outcome/months
Group A (n = 15)				
5	SG/T2N0	S	No	NED/24
1	SG/T1N1	S	No	NED/24
5	G/T2N0	S	No	NED/24
1	G/T2N1	S	No	NED/24
1	HP/T2N0	S	No	NED/24
1	HP/T1N0	S	No	NED/24
1	HP/T2N1	S	No	NED/24
Group B (n = 13)				
4	SG/T2N1	S	L, Reg	NED/24 (2), AWD/24 (2)
2	SG/T3N1	S	L	DOD/18, AWD/24
1	SG/T2N1	S	Reg	NED/24
3	G/T2N1	S	L, Reg	DOD/21 (1), AWD/24 (2)
1	HP/T1N1	S	Reg	NED/24
2	HP/T2N1	S	Reg	AWD/24 (2)
Group C (n = 9)				
1	SG/T2N2	S+POR	Reg	DOD/16
1	SG/T3N0	S+CHEM	L, Reg	AWD/24
1	G/T2N2	S+POR	Reg	DOD/14
1	HP/T1N2	S+POR	Reg	AWD/14
1	HP/T2N0	S+POR	L	AWD/24
1	HP/T3N0	S+POR	L	DOD/4
1	HP/T3N1	S+POR	L, Reg	DOD/6
1	HP/T4N2M1	R		DOD/2
1	HP/T3N3	R		DOD/4
Total n = 37 SG = 15 G = 10 HP = 12				

G = Glottis, SG = supraglottis, HP = hypopharynx, S = surgery, S+POR = surgery and postoperative radiation, R = radiation, L = local, Reg = regional, NED = no evidence of disease, DOD = death due to disease, AWD = alive with disease, CHEM = chemotherapy.

histamine levels have been analysed in patients with various solid neoplasms, but different results were obtained in two studies [6, 11].

In this study, the concentration of LBSA, histamine and PGE in the blood of patients with squamous cell carcinoma of the head and neck (SCCHN) were determined and changes in these parameters in various stages of the disease analysed.

PATIENTS AND METHODS

Patients

The LBSA, histamine and PGE levels were analysed in 37 patients undergoing therapeutic surgery or combined therapy for SCCHN at the ENT Department, School of Medicine, University of Zagreb (Table 1). Tumour diagrams and pathology reports were used to classify tumours according to site and stage. Clinical staging of malignant tumours was determined according to the recent UICC TNM classification (1987). The primary sites of carcinomas were: larynx 25 (glottis 10, supraglottis 15) and hypopharynx 12. There were 32 males and 5 females, aged 36–62 years (mean, 55 years). The analysis of PGE, LBSA and histamine concentrations showed no significant differences according to the primary site of carcinoma and data of all patients were, therefore, pooled. Surgery was performed in 35 patients (Table 1); in 28 patients it was the only treatment, while in 7 patients the excision was judged to be insufficient, and was combined with radiotherapy (6 patients) or chemotherapy (1 patient). For various reasons (extensive local or distant spread of tumour), surgery was not performed in 2 patients, who were treated with radiotherapy alone.

Tumour recurrence and survival of patients were followed-up for 24 months (Table 1). Out of 28 patients treated with surgery alone, 15 patients were tumour-free up to 24 months after surgery, whereas in 13 patients the tumour recurred locally or in regional lymph nodes. Clinically detectable tumour recurred in all 7 patients treated with a combination of surgery and radiotherapy. Generally, the recurrent tumours were surgically removed and/or treated with radiotherapy. Therefore, according

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to the treatment and final outcome, three different groups of patients could be studied: patients with resected primary tumours without tumour recurrence within 24 months (group A; $n = 15$), patients with resected primary tumours and tumour recurrence (group B; $n = 13$) and patients with partial or no surgical resection of tumour (group C; $n = 9$). The control population consisted of 12 hospitalised patients who were free of cancer, 10 males and 2 females aged 20–61 years (mean, 51 years) and of 10 normal subjects, 6 males and 4 females aged 18–26 years (mean, 21 years). Non-cancer patients were treated for otitis medmedia acuta (3), nodulus plicae vocalis (5) and defectus septi nasi (4).

Blood samples

Blood was obtained by antecubital vein puncture, collected into ice-cold tubes (3–5 ml) containing 250 U of heparin and 1 g/ml indomethacin. After centrifugation at 500 *g* for 10 min, plasma was separated and immediately stored at −22°C for PGE and LBSA determinations. For histamine detection, blood was immediately processed (see below). The values of all three parameters were determined within 20–60 days after sample storage. In cancer patients, blood samples were taken before surgical tumour resection and at least at one of the following time intervals after tumour resection: 15–30 days, 1–6 months, or more than 6 months (up to 2 years after operation).

PGE determination

PGE radioimmunoassay kit (Steranti, Herts, U.K.) was used for measuring PGE content in serum. Protein denaturation and PGE extraction from plasma were performed according to the manufacturer's instructions, as described in detail previously [11]. The sensitivity of this assay is 10 pg/ml PGE, and the intertest coefficient of variation <15%, as shown in our previous experiments [10].

Histamine determination

Histamine was extracted from blood by treatment with perchloric acid, as described elsewhere [12]. The supernatants were stored at +4°C until analysis, which was performed by the fluorometric method, using a Kontron spectrofluorometer SFM 23 and an automated continuous flow technique. This method has been routinely employed in one of our laboratories (Faculte Necker, Paris) and was found to be very reliable [6, 13].

LBSA determination

LBSA determination was performed according to the resorcinol method of Svennerholm and Fredman [14]. The sensitivity of this test in our laboratory was about 0.5 mol/l, and the intertest coefficient of variation (for 8 healthy controls not included in this study) was 6–8%.

Statistics

Since some data did not show normal distribution according to the Kolmogorov–Smirnov goodness of fit test, a Wilcoxon rank sum test was used for comparison of data in independent samples and Wilcoxon matched pairs signed rank test for paired samples [15]. The central tendency of data is expressed as medians, and variability by min–max ranges or by particular percentile values. Differences at a $P < 0.05$ level were considered significant.

RESULTS

PGE concentration

As shown in Fig. 1, the PGE concentration was somewhat higher in non-cancer patients (median 34.5 pg/ml, range 24.2–42.4) than in healthy subjects (median 28.75, range 21.2–34.5). In spite of a wide range of variability, the mean preoperative PGE level in the three groups of cancer patients was significantly higher ($P \geq 0.02$) than in healthy subjects:

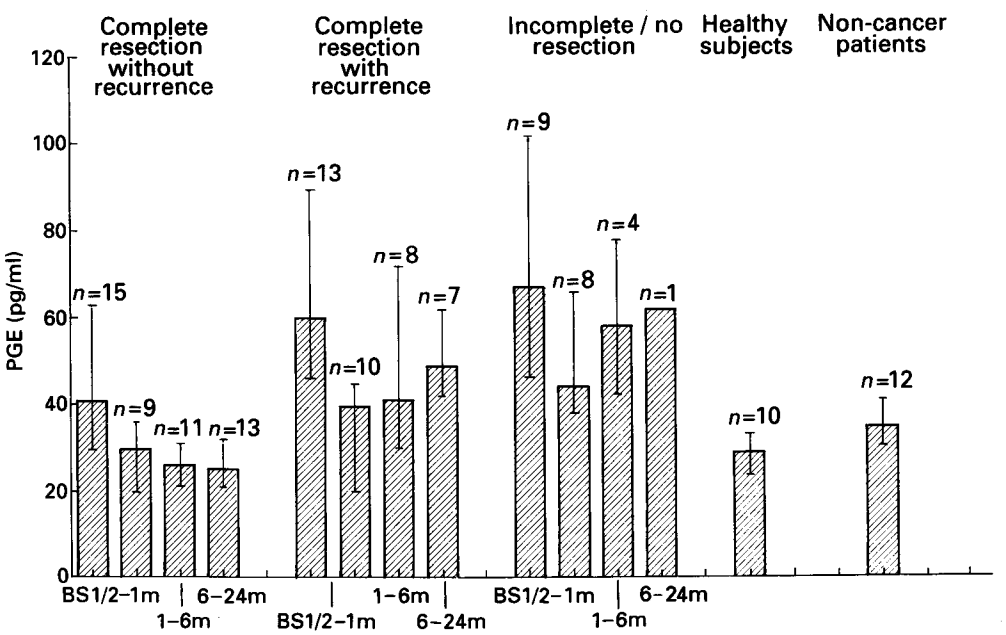

Fig. 1. Concentration of PGE in plasma of cancer patients, non-cancer patients and healthy subjects. The height of column represents median value and bars indicate the position of the first and third quartiles. Numbers above bars indicate the number of patients analysed at that time point. In cancer patients, preoperative and postoperative PGE levels are separately shown for three groups of patients: patients with complete tumour resection without tumour recurrence within 24 month (complete resection without recurrence), patients with complete tumour resection with tumour recurrences (complete resection with recurrence) and patients with incomplete or no tumour resection (incomplete/no resection). BS, before surgery; 1/2–1 m, determined 1/2 to 1 month after surgery; 1–6 m, 1–6 months after surgery; 6–24 m, 6–24 months after surgery.

median 41, range 13.8–85.8 in patients with complete tumour resection without recurrence (group A); median 60, range 24.8–129 in patients with complete tumour resection with tumour recurrence (group B); and median 67, range 26.5–127 in patients with incomplete or no tumour resection (group C). The preoperative PGE level in group A cancer patients was significantly higher than in groups B or C ($P = 0.042$ and $P = 0.027$, respectively), while there was no significant difference between groups B and C ($P = 0.71$).

Fifteen to 30 days after tumour resection, the PGE concentration decreased in all cancer patients, but the decrease was significant ($P < 0.01$ or higher) only in groups B and C. However, further changes in the PGE concentration were different in the three groups of cancer patients. Whereas in group A, the median PGE concentration steadily decreased to the level of healthy subjects, in groups B and C it rose again toward the preoperative level.

Sialic acid concentration

The concentration of LBSA was somewhat higher in non-cancer patients (median 24.95 mol/l, range 18.2–30.2) than in healthy subjects (median 20.1 mol/l, range 18.2–30.2), but the difference was not statistically significant ($P = 0.065$) (Fig. 2). Preoperatively, LBSA concentration in cancer patients was higher in group C (median 46.2 mol/l, range 30–80.9) or group B (median 47.3 mol/l, range 27.5–69.9) than in group A (median 33.3 mol/l, range 26–72.3), but these differences were not significant ($P = 0.21$ and $P = 0.29$, respectively). However, the LBSA concentration was significantly higher in all the three patient groups than in healthy subjects ($P < 0.001$ or higher). In the first month after tumour resection, the concentration of LBSA decreased in all groups of cancer patients, but this decrease was significant only in groups B and C ($P = 0.028$ and $P = 0.012$, respectively). However, 6 or more months after tumour resection, LBSA rose again in these two groups, whereas in group A it steadily decreased and reached normal range.

Histamine concentration

Blood histamine concentration was lower in non-cancer patients (median 60.5 ng/ml, range 35–102.5) than in healthy subjects (median 68.5 ng/ml, range 36–91); but, due to a high range of individual variations, the difference is not significant ($P = 0.23$) (Fig. 3). Preoperative concentrations of histamine in all the three groups of cancer patients (group A: median 56 ng/ml, range 18.5–86; group B: median 54 ng/ml, range 29.5–95; group C: median 49 ng/ml, range 18.5–108.5) were lower than in control groups, but not significantly ($P > 0.05$ in comparison to either control group). After surgical removal of the tumour, the concentration of histamine in group A rose to the normal range already within 15–30 days after tumour resection. The concentration of histamine in group B and C patients did not increase significantly within the first 6 months, but unexpectedly, it continued to rise later, approaching the normal values within 24 months.

Sensitivity of PGE, LBSA and histamine determination

Table 2 shows the incidence of elevated levels of PGE and LBSA and decreased levels of histamine in the blood of cancer patients. Data for each postoperative time, as well as pooled data for the whole postoperative period, are shown separately. The cut-off value was taken as a value higher than the 90 percentile value (PGE and LBSA) or lower than the 10 percentile value (histamine) in combined control groups (the data for healthy subjects and non-cancer patients were united, since there were no significant differences in the concentrations of either parameter in these subjects). For PGE, this value was 41.1 pg/ml, for LBSA 28.6 mol/l, and for histamine 36.3 ng/ml.

Preoperatively, PGE was elevated in 53.3, 84.6 and 88.9% cancer patients in groups A, B and C, respectively (total incidence of 67.6%). It was elevated also in 2/12 (16.7%) non-cancer patients, but in none of 10 healthy controls. Fifteen to 30 days after operation, the incidence of elevated values dropped in all groups of cancer patients. However, with increase in postoperative time, this incidence further decreased in group A patients (total postoperative incidence of elevated values 6.1%), whereas in groups B and C it increased again (total incidence of increased values 56.0 and 76.9%, respectively).

Preoperatively, LBSA was elevated in a much higher percentage of cancer patients than PGE (92.9 in group A, 92.3 in group B and 100% in group C; total incidence 94.4%). The

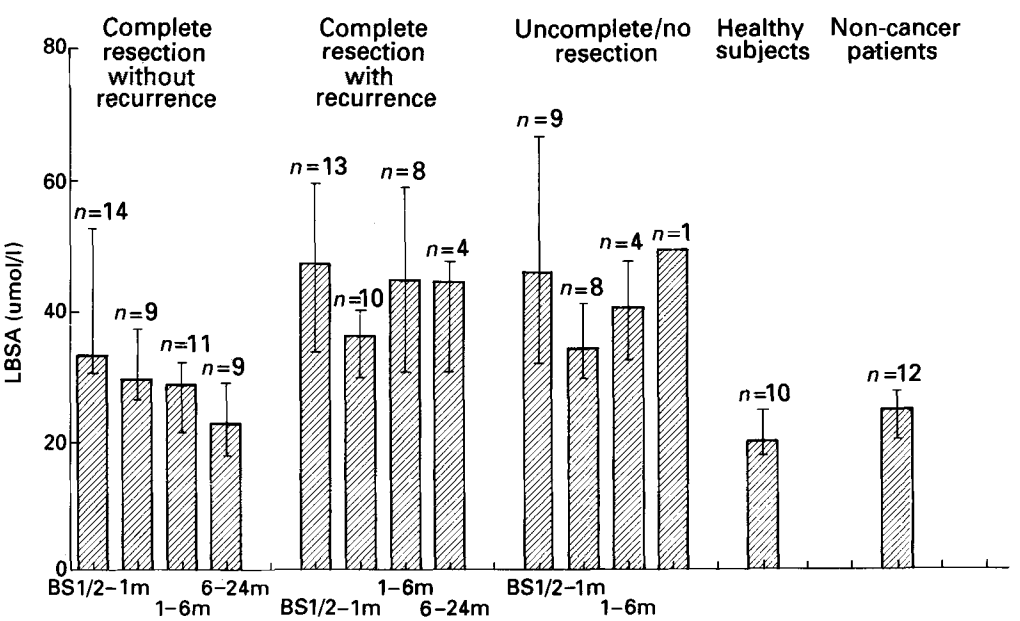

Fig. 2. Concentration of serum LBSA in cancer patients and healthy subjects (see legend to Fig. 1).

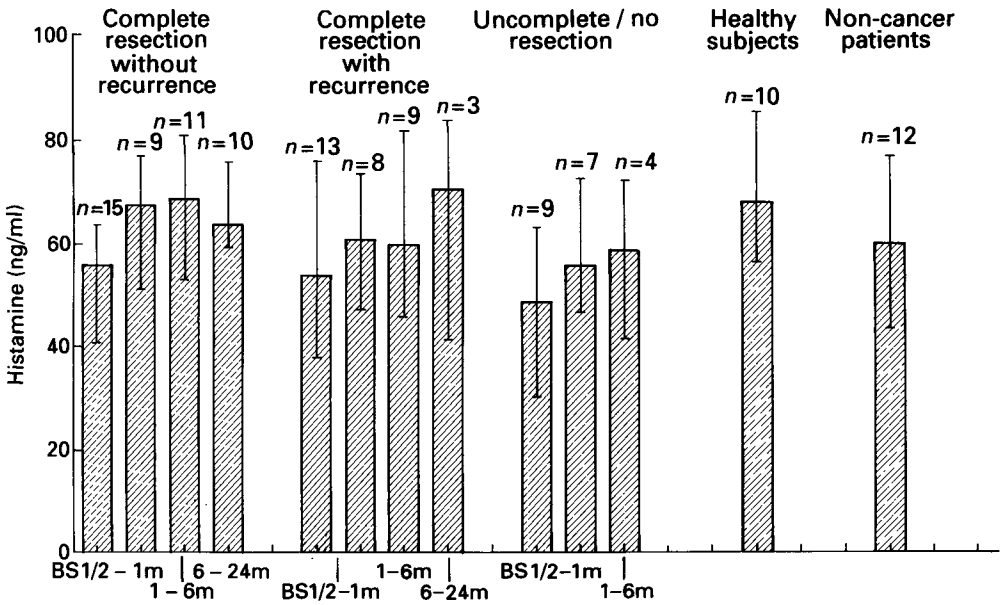

Fig. 3. Concentration of histamine in blood of cancer patients, non-cancer patients and healthy subjects (see legend to Fig. 1).

concentration of LBSA was elevated in 2/12 (16.7%) of non-cancer patients and in none out of 10 healthy subjects. The postoperative decrement of elevated LBSA levels in group A of cancer patients was much slower and less expressed than it was in the case for PGE. In group B and C of cancer patients, there was small decrease or almost no change, respectively, in incidence of elevated LBSA levels after operation. Total incidence of elevated LBSA levels at all time postoperatively was 55.2, 87.0 and 92.3% in groups A, B and C, respectively.

The incidence of decreased preoperative levels of histamine in cancer patients was very low; 20, 23.1 and 33% in groups A, B and C, respectively. It was decreased in 1/12 (8.3%) and in none of 10 healthy subjects. Postoperatively, no cancer patient from any group had a decreased level of histamine.

DISCUSSION

There are many data showing that prostaglandins of series E, especially PGE_2, might promote tumour growth. PGE suppress many immunological reactions [16–18], and this suppression can be partially or completely abolished by addition of indome-

Table 2. The sensitivity of PGE, LBSA and histamine determination

Group	No. of patients with abnormal concentration/Total no. of patients (%)														
	PGE (>41 pg/ml)*					LBSA (>28.62 nmol/l)*					Histamine (<36.3 ng/ml)†				
		After operation					After operation					After operation			
Cancer patients	Bef. op.‡	1/2–1 mo	1–6 mo	6–24 mo	Total	Bef. op.‡	1/2–1 mo	1–6 mo	6–24 mo	Total	Bef op.‡	1/2–1 mo	1–6 mo	6–24 mo	Total
A. Complete tumour resection without recurrence (n = 15)	8/15 (53.3)	1.9 (11.1)	0/11 (0)	1/13 (7.7)	2/33 (6.1)	13/14 (92.9)	7/9 (77.8)	6/11 (54.5)	3/9 (33.3)	16.29 (55.2)	3/15 (20)	0/9 (0)	0/11 (0)	0/10 (0)	0/30 (0)
B. Complete tumour resection with recurrence (n = 13)	11/13 (84.6)	4/10 (40)	4.8 (50)	6/7 (85.7)	14/25 (56.0)	12/13 (92.3)	10/10 (100)	7/8 (87.5)	3/5 (75)	20/22 (87.0)	3/13 (23.1)	0/8 (0)	0/9 (0)	0/3 (0)	0/20 (0)
C. Incomplete/no resection (n = 9)	8/9 (88.9)	6/8 (75)	3/4 (75)	1/1 (100)	10/13 (76.9)	9/9 (100)	7/8 (87.5)	4/4 (100)	1/1 (100)	12/13 (92.3)	3/9 (33.3)	0/7 (0)	0/4 (0)	–	0/11 (0)
Non-cancer patients (n = 12)	2/12 (16.7)					2/12 (16.7)					1/12 (8.3)				
Healthy patients (n = 10)	0/10 (0)					0/10 (0)					0/10 (0)				

*Value equal or higher than 90th percentile of pooled data from healthy subjects and non-cancer patients.
†Value equal or lower than 10th percentile of pooled data from healthy subjects and non-cancer patients.
‡Bef. op, before operation; mo, months.

thacin, a prostaglandin synthesis inhibitor. In some studies tissue content or plasma level of PGE correlated with the aggressiveness and spread of tumour [8, 11, 19, 20]. In head and neck cancer, tissue content of PGE was higher in tumour than in normal tissue [21, 22]. Similarly, it was shown that growth or metastatic potency of a mouse cancer cell line correlates with its ability to produce PGE_2 *in vitro* [23].

Our results show that the plasma concentration of PGE correlates with the presence of tumour. The mean plasma PGE concentration was significantly higher preoperatively in all the three groups of cancer patients than in either non-cancer patients or healthy controls. Furthermore, it significantly decreased after surgical tumour removal, but it appeared to increase again in patients in whom tumour recurred after surgery (Fig. 1). These data support our previous findings [10] that the determination of plasma PGE level might have a prognostic significance.

LBSA has also been shown to increase in patients with cancer and also some non-cancer diseases [3, 4, 24]. The increased serum LBSA might be due to the increased shedding or secretion of LBSA from tumour cell membrane, containing much more sialic acid than the membrane of normal cells [4, 24]. Levels also decrease after tumour resection [4, 5] and may correlate with the incidence of tumour metastases and tumour recurrences [5].

Similarly to PGE, the mean plasma LBSA concentration in our experiments was significantly higher in cancer patients than in non-cancer patients or healthy subjects (Fig. 2). However, after surgical removal of tumour it decreased until it was lower than PGE; a significant decrease of LBSA concentration in patients without tumour recurrence was reached at 6 or more months after tumour removal. In patients with tumour recurrences or in patients with partial tumour resection, mean postoperative reduction of LBSA concentration was only transient. Other investigators [24] have observed rapid normalisation of LBSA serum levels in mice after mammary carcinoma resection, whereas in humans with the same tumour this normalisation was more protracted.

Blood histamine level has also been shown to be a good marker for the progression of the cancer, being lower in patients with unresected primary tumours or tumour metastases than in normal subjects or in patients with resected tumour [6]. There was also some success in the treatment of advanced cancer with combined administration of histamine and its H2-receptor antagonist [13].

Our results generally do not support the above cited findings. Although the mean preoperative histamine concentrations in cancer patients were lower than in control groups, the differences were not significant (Fig. 3). Also, due to a relatively small preoperative change in the histamine level in cancer patients, the postoperative changes were insignificant and inconclusive.

Somewhat higher levels of PGE and LBSA and lower levels of histamine in non-cancer patients than in healthy subjects, observed in our experiments, could be explained by the fact that the non-cancer group included some patients with inflammatory diseases which may have influenced these parameters. Similar differences for all the three parameters were also observed by others [4, 6, 23]. This emphasises the importance of selecting appropriate controls in hospitalised non-cancer patients.

Analysis of the validity (sensitivity and specificity) of the three parameters tested as diagnostic markers (Table 2) showed that serum LBSA is the most sensitive and specific marker for the detection of a growing tumour. Regarding the preoperative LBSA level (93–100% sensitivity and 77–83% specificity), our results are similar to those of Katopodis *et al.* [3], who have demonstrated a high sensitivity (77–97%) and specificity (81–93%) of the test in a much higher number of patients with various cancers. In another study [4], LBSA was preoperatively increased in 85% of patients. However, after surgical removal of tumour LBSA was still elevated in a significant proportion of patients (55%) who were apparently tumour-free. This diminishes the validity of the test for the discrimination of these patients from patients with incomplete removal of tumour or patients with tumour recurrence.

The determination of plasma PGE concentration, although less sensitive (53–89% sensitivity before operation), appeared to be a better test in this respect. Generally, this study showed PGE to be a reasonable marker for the postoperative course of cancer disease, i.e. it was elevated in a high percentage of patients with tumour recurrence and in patients with treatment failure and in a much smaller proportion of patients who were apparently tumour-free.

The decrease of histamine blood content with cancer progression in our study was not as significant as previously reported [6]. The preoperative concentration was decreased in only 20–33% of patients, and postoperative levels did not discriminate patients with different courses of the disease. The reason for this discrepancy might be that head and neck tumours mainly spread and metastasise locally, whereas in the quoted study the tumours that spread readily and metastasise distally were analysed. Similarly, our results do not support the recent findings of Moriarty *et al.* [11], who found unchanged or even increased histamine levels in patients with solid malignant tumours.

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A Prognostic Score for Patients Resected for Gastric Cancer

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This paper describes the construction, validation and use of a simple prognostic score suitable for predicting survival of patients undergoing a curative gastric resection. Using death from all causes as outcome, the prognostic significance of age, sex, tumour site, stage of disease (nodal status and wall invasion), surgical treatment and histological type was investigated in a set of 213 patients recruited in a multi-centre clinical trial. A Weibull multiple regression model was adopted to evaluate the joint effect of these variables on survival. From a full model, containing all the variables, a final parsimonious model was obtained by means of a backward selection procedure. The prognostic score is based on the final model, including four variables which are easily detected in every institution: age, wall invasion, site of tumour, and nodal status. Three groups of patients with different probabilities of surviving 5 years from surgery were identified: group I (survival probability $\geq$ 70%), group II (30%–69%) and group III (< 30%). The prognostic score, obtained from the multicentre trial patients, was tested on a set of 135 consecutive patients in an independent institution, confirming its reliability in predicting survival. The score system presented can supply a simple tool for classifying patients radically operated for gastric cancer into three well discriminated groups from the prognostic point of view.
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INTRODUCTION

THE KNOWLEDGE of prognostic factors in patients with gastric cancer has a pivotal importance in clinical practice: in the single patient it enables improved assessment of the benefit–risk ratio and in clinical research it enables one to select prognostically homogeneous groups of patients better to assess the effectiveness of different therapeutical strategies.

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Most of the data regarding prognosis are obtained from analyses of putative prognostic factors in a univariate fashion. However, in the presence of many factors, especially when they are correlated, this method fails to detect the contributory role of the single variable to the prognosis. Therefore, the information attained has a limited value and much attention has recently been given to multivariate analyses.

We previously focused our interest [1] on various prognostic variables which have been widely investigated in the literature and are easily detected in all patients who undergo a curative gastric resection; their prognostic value is confirmed not only in univariate, but also in multivariate analyses. They include: age of patient [1, 2] depth of neoplastic invasion of the gastric wall [1–5], site in the stomach where the tumour is situated [6, 7] and nodal involvement [1, 2, 5, 8]. Moreover, we argued that it would be possible to define more precisely the survival experience of patients by considering these variables overall.