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DYNAMICS OF THE VENOUS BLOOD ACID-BASE BALANCE AND RELATIONSHIP BLOOD pH Vs TUMOR IN LARYNGEAL CANCER PATIENTS

Динаміка кислото-основного балансу венозної крові та взаємовідносини pH крові та пухлини у хворих на рак гортані

Abstract

The characteristic for most solid tumors cells is the intracellular alkalinization and acidification of the extracellular milieu and this pH gradient inversion (pHe < pHi) is associated with tumor proliferation, invasion, metastasis, aggressiveness, and treatment resistance. However is there tumor pH (pHi and/or pHe) changes affect on venous blood plasma pH?

Purpose of the study. *The venous blood acid-base balance before and after the combined treatment, correlation of the venous blood pH indicators (pHb), relationship neoplasm and blood pH in patients with laryngeal cancer was study.*

Material and methods. *Studies were performed in patients with laryngeal cancer categories T2–3 N0 M0 before and after the combined treatment. The patients were divided into four groups: Group 1 – 25 patients before the start of treatment; Group 2 – 21 patients (from Group 1) after completion of the combined treatment; Group 3 – 14 patients from Group 2 with positive results of treatment and Group 4 – 7 patients from Group 2 with a negative result of treatment (recurrence and/or metastasis of the neoplasm). The control group consisted of 15 practically healthy people (Group C).*

Examination of venous blood acid-base balance of patients, tumor pH and tumor cells pHi and pHe was carried.

Results and discussion. *The increase in pCO_2 and HCO_3^- concentration will result in decrease in the pH, but if these indicators have a clear correlation in the control group, then in patients*

Резюме

Для більшості солідних пухлин характерно підвищення pH цитоплазми клітин (pHi > 7,2) та підкислення позаклітинного середовища (pHe ≈ 6,2–7,1). Зворотний pH градієнт ракових клітин (pHe < pHi) пов'язують з проліферацією, інвазією, метастазуванням та агресивністю пухлин але на цій особливості новоутворень розробляються і стратегії для підвищення ефективності їх лікування.

Мета дослідження. *Вивчити кислотно-основний баланс венозної крові до і після комбінованого лікування, кореляцію показників pH венозної крові, взаємозв'язок новоутворення та pH крові у хворих на рак гортані.*

Матеріали та методи. *Дослідження виконані у хворих на рак гортані категорій T2–3 N0 M0 до і після комбінованого лікування (період спостереження 2012–2018, період особистого спостереження не менше трьох років). Вік пацієнтів коливався від 34 до 65 років. Морфологічна характеристика новоутворень – зроговіла плоскоклітинна карцинома.*

Хворі були розділені на чотири групи: група 1 – 25 пацієнтів до початку лікування; група 2 – 21 хворий (з групи 1) після завершення комбінованого лікування; група 3 – 14 пацієнтів з групи 2 з позитивними результатами лікування; група 4 – 7 хворих з групи 2 з негативним результатом лікування (рецидив та/або метастазування новоутворення).

Контрольну групу (група С) склали 15 практично здорових чоловіків того ж віку.

Проведено дослідження кислотно-основно-

groups there was a correlation for pHb & pCO_2 and pO_2 only. Besides, we marked increase in pCO_2, HCO_3^-, K^+, while pO_2 decreased in pHb after the combined treatment.

It is necessary to point out the differences between some benchmarks and indicators of acid-base balance in the plasma of venous blood in primary patients and patients with recurrent laryngeal cancer. So, if pHb, pO_2, and Cl^- patients have statistically significant differences from control data, then differences with control pCO_2 values are characteristic only for patients of Groups 1 and 3. On the contrary, differences in the HCO_3^- indices are characteristic only for patients of Group 4. There are statistically significant differences from the control indicators K^+, Na^+, Ca^{2+}, Glu, Lac, mOsm in patients of the first group and Cl^- and Lac of patients in the third group. Among the indicators in the third and fourth groups of patients, statistically significant differences were noted in the values of pHb, HCO_3^- and Glu.

In patients of groups 1 and 4, the determination of pHt and the calculation of pHi, pHe revealed decrease in pHt and pHe with increasing pHi in patients with recurrence of the neoplasm.

The final stage of the study was to determine the relationship (and not correlation) of blood pH and laryngeal tumors and the relationship was noted in the «pHb-tumor» system in primary patients, but in patients in 3 and 4 Groups, that «pHb-tumor» connection is rather contradictory.

Conclusion. *Acid-base balance indicators obviously cannot be considered as unconditional markers of carcinogenesis, but their monitoring and, in particular, venous blood pH, of patients after special treatment, can help determine the risk group of patients who may develop of a malignant neoplasm recurrence.*

Keywords: *acid-base balance, laryngeal cancer, relapse, prognosis.*

го балансу венозної крові хворих. Визначений pH пухлин (pHt) з подальшим розрахунком pH цитоплазми клітин та pH позаклітинного середовища.

Результати та обговорення. *Після завершення комбінованого лікування відзначено зниження pH плазми крові (pHb) та pO_2 при збільшені значень показників pCO_2, HCO_3^- і K^+. При порівнянні даних першої та третьої групи відмінності були відзначені лише в показниках Ca^{2+} але порівняння даних першої та четвертої групи показало значущі відмінності показників pHb, pO_2, HCO_3^- і mOsm.*

Збільшення концентрації pCO_2 і HCO_3^- призводе до зниження pH, але якщо ці показники мали чітку кореляцію в контрольній групі, то в першій, другій та третій групах кореляція відмічена лише для pHb/pCO_2 і pHb/pO_2. У четвертій групі суттєвих кореляцій цих показників не відмічено.

Разом з тим, у пацієнтів 1 і 4 групи визначення pHt і розрахунок pHi, pHe виявили зниження pHt і pHe зі збільшенням pHi у пацієнтів з рецидивом новоутворення. Можливо це пояснює той факт, що кисле середовище мікрооточення сприяє прогресуванню пухлини – ацидоз, токсичний для нормальних клітин, сприяє деградації позаклітинного матриксу, але самі аномальні клітини стають менш вразливими.

Слід вказати на відмінності деяких контрольних показників і показників кислотно-лужного балансу в плазмі крові у первинних хворих і хворих з рецидивом раку гортані. Так, якщо показники pHb, pO_2 и Cl^- хворих мають статистично значущі відмінності від контрольних даних, то відмінність з контрольними значеннями pCO_2 характерна лише для хворих першої і третьої групи. Навпаки, відмінності показників HCO_3^- характерні лише для хворих четвертої групи. Мають статистично значущі відмінності від контрольних показники K^+, Na^+, Ca^{2+}, Glu, Lac, mOsm хворих першої групи і Cl^-и Lac хворих третьої групи. Серед показників в третій і четвертій групах хворих статистично значущі відмінності відзначені в значеннях показників pHb, HCO_3^- и Glu. При цьому, визначено наявність причинно-наслідкового зв'язку в системі «пухлина-pHb» у первинних хворих, але у хворих з рецидивом захворювання залежність «пухлина–pHb» має досить суперечливий характер.

Висновок. *Показники кислотно-основного балансу не можна розглядати як безумовні маркери канцерогенезу але їх моніторинг і зокрема pH венозної крові може допомогти визначити групу ризику серед пацієнтів, у яких може розвинутися рецидив злоякісного новоутворення.*

Ключові слова: *кислотно-основний баланс, рак гортані, рецидив, прогнозування.*

INTRODUCTION

Cells population growth is determined by the genetic program of metabolism, wherein cells, for the order to function optimally, must constantly maintain an intracellular pH within a narrow range (pHi = 7,1–7,2) through the activity of transporters located at the plasma membrane. These transporters can be modulated by endogenous or exogenous molecules and pHi changes have been implicated in both cell proliferation and cell death. Notably, if the intracellular alkalinization is a common feature of proliferative processes, then the intracellular acidification has the cytotoxic effect through of apoptosis induction [1–3]. But for most cells of solid tumors characterized by the presence of intracellular alkalization of the cytoplasm (pHi > 7,2) and acidification of the extracellular milieu (pHe = 6,5–7,1) – a reverse pH gradient in cancer cells, unlike similar indicators of normal cells: pHi ≈ 7,2, pHe ≈ 7,4 [4–8]. The acidification environmental tumors occurs already on early in cancers (cancer in situ), during the avascular phase, and pH gradient inversion (pHe < pHi) is associated with tumor proliferation, invasion, metastasis, aggressiveness, and treatment resistance [8–10].

Currently, it is believed that pH inversion, like hypoxia, is a common symptom of cancer and on this peculiarity of tumors various strategies are being built to increase the effectiveness of their treatment [11–18], but individual tumors may be had both positive and negative (reverse) pH gradients [19]. But still, the relationship between extracellular and intracellular pH are dependent upon the pH range. Intracellular pH was relatively resistant to a change in extracellular pH over the pHe range of 6,8 to 7,8 (i.e., delta pHi congruent to delta pHe × 0,33) [20]. However is there tumor pH (pHi and/or pHe) changes affect on venous blood plasma pH?

PURPOSE OF THE STUDY

The venous blood acid-base balance before and after the combined treatment, correlation of the venous blood pH indicators, relationship neoplasm and blood pH in patients with laryngeal cancer was study.

MATERIAL AND METHODS

Studies were performed in patients with laryngeal cancer categories T2–3 N0 M0 before and after the combined treatment (observation period 2012–2018, personal observation period after the combined treatment of at least three years). The age of the patients ranged from 34 to 65 years. The neoplasms morphological characteristic is keratinizing squamous cell carcinoma.

The patients were divided into four groups:

– Group 1 – 25 patients before the start of treatment.

– Group 2 – 21 patients (from Group 1) after completion of the combined treatment.

– Group 3 – 14 patients from Group 2 with positive results of treatment.

– Group 4 – 7 patients from Group 2 with a negative result of treatment (recurrence and/or metastasis of the neoplasm).

The control group consisted of 15 practically healthy people (Group C) of the same age.

Laboratory researches:

1. Examination of venous blood acid-base balance of patients with laryngeal cancer was carried – pH and pCO_2, pO_2 (mm/Hg), HCO_3^-, K^+, Na^+, Ca^2, CL^-, Glu, Lac, mOsm (mmol/l).

2. To the small (≈ 2–2,5 mm^3) crushed tumor fragment was added 0,5 ml of H_2O (pHconst = 7,328), the pH of the suspension was measured, which was regarded as the pH of the tumor.

3. Calculation of the pHi and pHe indicators was carried out according to the formula:

$$pHi = pHconst + [2 \times (pHconst - pHt)] \times 0,33$$

$$pHe = pHt - (pHi - pHconst)$$

Comparisons of the studied parameters were carried out using the Wilcoxon Matched Pairs Test, Wald-Wolfowitz Runs Test and Spearman Rank Order Correlations, at the critical significance level of 0,05. The analyzed data are presented as «median and interquartile interval»: Me (RQ = UQ–LQ). The causal relationship between the indicators was evaluated using multiple logistic regression analysis. Statistical processing of the received data was made using computer programs of the STATISTICA package (StatSoft Statistica v.7.0).

RESULTS AND DISCUSSION

The data of pH venous blood plasma (pHb) of patients, before the beginning and after treatment in table 1 are present.

The change in plasma pH in patients after treatment (7,35 → 7,31; p = 0,071) is not statistically significant, but it is important from a clinical point of view. But it should be noted, that all changes pH occur through changes in three independent variables – carbon dioxide, relative electrolyte concentrations, and total weak acid concentrations and some of these characteristics change and have statistically significant differences in groups 1 and 2 (increase in pCO_2 46,08 → 48,8; HCO_3^- 24,9 → 26,0 and K^+ 3,95 → 4,5, while pO_2 decreased 37,98 → 23,63) [21].

However, the patients in Group 2 had both positive (14 patients, who third Group constituted)

and negative (7 patients) treatment results (Group 4). Moreover, when comparing the data of the first and third groups, statistically significant spills are noted in Ca^{2+} indicators only (1,14 → 1,25), while comparing the data of the first and fourth groups, significant differences were observed in indicators of pHb (7,35 → 7,22) pO_2 (37,98 → 20,0), HCO^-_3 (24,9 → 22,2) и mOsm (284,1 → 288,4).

It is known, that increase in pCO_2 and HCO_3^- concentration will result in decrease in the pH [21]:

$$pH = pK \times \log [HCO_3^- / (0{,}03 \times pCO_2)]$$

But if these indicators have a clear correlation in the control group, then in 1, 2, 3 groups of patient there was a correlation for pHb & pCO_2 and pHb & pO_2 and no correlation for pHb & HCO_3^-, and in the fourth group the insignificant correlation was noted for pHb & pCO_2 and pHb & pO_2 (table 2).

Table 1

The acid-base balance indicators in the venous blood plasma of patients

Test	Group (Me; RQ = UQ–LQ)				p-level
	Group 1 (n = 25)	Group 2 (n = 21)	Group 3 (n = 14)	Group 4 (n = 7)	
pHb	7,35 7,42 – 7,31 =0,11	7,31 7,34 – 7,31 = 0,03	7,32 7,38 – 7,31 = 0,07	7,29 7,31 – 7,26 = 0,05	×0,071 +0,509 *0,091
pCO_2 mm/Hg	46,08 47,1 – 42,2 = 4,9	48,8 53,8 – 48,7 = 5,7	48,8 49,2 – 47,9 = 1,3	56,1 62,9 – 48,7 = 14,2	×0,027 +0,331 *0,018
pO_2 mm/Hg	37,98 49,95 – 35,0 = 14,95	23,63 29,4 – 19,0 = 10,4	29,0 32,0 – 19,0 = 13,0	19,0 20,0 – 14,1 = 5,9	×0,002 +0,096 *0,063
HCO^-_3 mmol/l	24,9 25,19 – 24,65 = 0,54	26,0 28,7 – 25,1 = 3,6	25,02 26,0 – 24,8 = 1,2	25,8 29,0 – 20,7 = 8,3	×0,017 +0,272 *0,799
K^+ mmol/l	3,95 4,13 – 3,9 = 0,23	4,5 5,1 – 4,1 = 4,0	4,35 5,0 – 4,0 = 1,0	4,9 5,2 – 4,5 = 0,7	×0,009 +0,101 *0,063
Na^+ mmol/l	140,0 140,4 – 139,5 = 0,86	140,0 142,0 – 139,0 = 3,0	139,5 142,0 – 139,0 = 3,0	139,4 144,0 – 139,0 = 5,0	×0,972 +0,949 *0,554
Ca^{2+} mmol/l	1,14 1,2–1,07 = 0,13	1,19 1,26 – 1,17 = 0,09	1,25 1,27–1,18 = 0,09	1,22 1,27 – 1,0 = 0,27	×0,106 +0,041 *0,866
Cl^- mmol/l	107,0 109,0 – 107,0 = 2,0	108,0 109,0 – 107,7 = 1,3	109,0 109,0 – 104,0 = 5,0	108,0 111,0 – 108,0 = 3,0	×0,834 +0,529 *0,753
Glu mmol/l	5,5 5,7 – 4,9 = 0,8	5,5 5,9 – 5,2 = 0,7	5,15 5,9 – 4,7 = 1,2	5,5 5,9 – 5,2 = 0,7	×0,768 +0,754 *0,463
Lac mmol/l	1,65 1,81 – 1,5 = 0,31	1,8 2,2–1,6 = 0,6	1,75 2,2 – 1,5 = 0,7	2,0 2,3 – 1,5 = 0,8	×0,112 +0,379 *0,643
mOsm mmol/l	284,1 284,5 – 283,8 = 0,7	285,6 289,1 – 283,0 = 6,1	284,05 289,1 – 282,0 = 7,1	288,0 291,5 – 284,5 = 7,0	×0,395 +0,638 *0,176

Note: *×p-level for G1 Vs G2 groups; +p-level for G1 Vs G3 groups; *p-level for G1 Vs G4 groups*

Table 2

Correlations between plasma pH and pCO_2, pO_2 and HCO_3^- in control and in groups of patients

Spearman Rank Order Correlations	Groups									
	GC		G1		G2		G3		G4	
	R	p	R	p	R	p	R	p	R	p
pHb & pCO_2	0,53	0,042	–0,75	0,0001	–0,61	0,003	–0,74	0,002	–0,39	0,378
pHb & HCO_3	0,56	0,029	–0,14	0,499	0,34	0,003	–0,07	0,819	–0,18	0,699
pHb & pO_2	0,72	0,0003	0,65	0,001	–0,61	0,003	0,91	0,000	0,38	0,398

Changes in blood pH induce powerful regulatory effects at the level of the cell, organ, and organism, but how tumor pH (pH of cytoplasm + interstitial fluid) does it affect on blood pH and whether and to what extent it is possible to consider its dynamics as a predictor of the course of the disease or as performance evaluation of cancer patients treatment. However, we should highlight a few problems, associated with both the tumor and its microenvironment [7, 19–27].

Firstly, the resting pHi of a cell can be defined as the steady-state point at which net metabolic acid production is balanced by net membrane H^+/H^+-equivalent transport. But these fluxes to show considerable regional variation in solid tumors, resulting in the potential for large pHi gradients alongside pHe non-uniformity.

Second, tumor histology and tumor volume is the most important factors determining the range of pHe's. A combination of poor vasculature perfusion, regional hypoxia and increased flux of carbons through fermentative glycolysis leads to extracellular acidosis in solid tumors, with extracellular pH values as low as 6,5, but overall, actual pH in squamous cell carcinomas is 7,20 ± 0,07 (pHt in range 6,2–7,6) with the pHi and pHe values lying mostly in the range 7,1–7,65 and 6,2–6,9 respectively [28–32].

Thirdly, tissue pH is difficult to investigate by measuring pH in cells suspensions or monolayers prepared from cultured cells. Besides no equations which would allow accurate calculation of indicators pHi or pHe based on the pHt indicator. Rather, these calculations will confirm the trend – pHi and pHe will change in opposite directions (extracellular acidification and intracellular alkalinization).

In patients of groups 1 and 4, the determination of pHt and the calculation of pHi, pHe revealed decrease in pHt and pHe with increasing pHi in patients with recurrence and/or metastasis of the neoplasm (table 3). Obviously this can be explained by surviving in treatment tumor cells begin to actively proliferate and the acidic environment of the microenvironment contributes to tumor progression, stimulating invasion and metastasis, acidosis can be toxic to normal cells and mediate degradation and remodeling of the extracellular matrix, can enhance angiogenesis due to release of vascular endothelial growth factor, but themselves abnormal cells become less vulnerable [31, 33–37].

Table 3

Tumor pH indicators in patients of the 1 and 4 groups

Test	Group (Me; RQ = UQ–LQ)		p-level
	Group 1 (n = 25)	Group 4 (n =7)	
pHt	7,05 7,09–7,02 = 0,07	6,98 7,035–6,915 = 0,12	0,002
pHe	6,87 6,852–6,712 = 0,14	6,75 6,742–6,502 = 0,24	0,002
pHi	7,51 7,636–7,596 = 0,04	7,56 7,741–7,621 = 0,12	0,057

It is necessary to point out the differences between some benchmarks and indicators of acid-base balance in the plasma of venous blood in primary patients and patients with recurrent laryngeal cancer. So, if pHb, pO_2, and Cl^- patients have statistically significant differences from control data, then differences with control pCO_2 values are characteristic only for patients of Groups 1 and 3. On the contrary, differences in the HCO_3^- indices are characteristic only for patients of Group 4. There are statistically significant differences from the control indicators K^+, Na^+, Ca^{2+}, Glu, Lac, mOsm in patients of the first group and Cl– and Lac of patients in the third group. Among the indicators in the third and fourth groups of patients, statistically significant differences were noted in the values of pHb, HCO_3^- and Glu (table 4).

Thus, the presented data indicate the presence of significant discrepancies in the control values of a number of indicators of acid-base balance and indicators of acid-base balance of patients who successfully completed treatment, from the corresponding indicators of primary patients and patients with recurrent neoplasm.

However, how pHb is coupled to cancer cell growth? The final stage of the research was the determination of the relationship (not correlation) of blood pH and laryngeal tumors and it is necessary to recall that the odds ratio (OR) from 0 to 1 indicates a low probability of the event being investigated, the OR of 1 means that the likelihood of an event is the same in both groups. The greater the odds ratio unit, the more likely it is to expect an even to develop (table 5). The analysis is carried out in groups G1 & GC, G4 & GC and G3 & G4.

From the data presented in the table indicate the presence of a causal relationship in the «pHb – tumor» system in primary patients, but in patients in 3 and 4 Groups, the «pHb – tumor» connection is rather contradictory. Obviously, this can be explained both by the presence of a progressive neoplasm and by the aggressive nature of the treatment methods carried.

Table 4

The acid-base balance indicators in the venous blood plasma in the control group and in the first, third and fourth group patients

Test	Group (Me; RQ = UQ–LQ)				p-level
	Group C (n = 15)	Group 1 (n = 25)	Group 3 (n = 14)	Group 4 (n = 7)	
pHb	7,39 7,41–7,36 = 0,05	7,35 7,42 – 7,31 =0,11	7,32 7,38 – 7,31 = 0,07	7,22 7,31 – 7,11 = 0,2	*0,002 ×0,038 +0,0001 °0,003
pCO_2	46,7 48,2 – 45,8 = 2,4	46,08 47,1 – 42,2 = 4,9	48,8 49,2 – 47,9 = 1,3	48,8 58,8 – 48,3 = 10,5	*0,000 ×0,038 +0,299 °0,673
pO_2	44,2 45,5 – 42,5 = 3,0	37,98 49,95 – 35,0 = 14,95	29,0 32,0 – 19,0 = 13,0	20,0 22,5 – 19,0 = 3,5	*0,000 ×0,0007 +0,0001 °0,353
HCO_3^-	24,1 25,0 – 24,1 = 0,9	24,9 25,19 – 24,65 = 0,54	25,02 26,0 – 24,8 = 1,2	22,2 23,8 – 20,7 = 3,1	*0,266 ×0,574 +0,040 °0,052
K^+	4,7 5,0 – 4,4 = 0,6	3,95 4,13 – 3,9 = 0,23	4,35 5,0 – 4,0 = 1,0	4,9 5,2 – 4,5 = 0,7	*0,005 ×0,347 +0,982 °0,151
Na^+	142,0 144,0 – 140,0 = 4,0	140,0 140,4 – 139,5 = 0,86	139,5 142,0 – 139,0 = 3,0	139,2 144,0 – 139,0 = 5,0	*0,032 ×0,347 +0,628 °0,933
Ca^{2+}	1,28 1,31 – 1,24 = 0,07	1,14 1,2–1,07 = 0,13	1,25 1,27–1,18 = 0,09	1,25 1,31 – 1,02 = 0,29	*0,032 ×0,187 +0,628 °0,151
Cl^-	105,0 107,0 – 102,0 = 5,0	107,0 109,0 – 107,0 = 2,0	109,0 109,0 – 104,0 = 5,0	109,0 111,0 – 108,0 = 3,0	*0,013 ×0,038 +0,040 °0,353
Glu	4,7 5,1 – 4,4 = 0,7	5,5 5,7 – 4,9 = 0,8	5,15 5,9 – 4,7 = 1,2	5,9 5,9 – 5,2 = 0,7	*0,072 ×0,574 +0,040 °0,544
Lac	2,1 2,4 – 1,9 = 0,5	1,65 1,81 – 1,5 = 0,31	1,75 2,2 – 1,5 = 0,7	2,0 3,2 – 1,5 = 1,7	*0,032 ×0,038 +0,319 °0,933
mOsm	288,0 291,1 – 286,0 = 5,1	284,1 284,5 – 283,8 = 0,7	284,05 289,1 – 282,0 = 7,1	288,4 290,0 – 284,5 = 5,5	*0,000 ×0,187 +0.077 °0,673

***Note:** *p-level for GC vs G1 groups; ×p-level for GC Vs G3 groups; +p-level for GC Vs G4 groups; °p-level for G3 Vs G4 groups*

Table 5

Relationship of the progressive tumors and venous blood plasma pH, pCO_2, pO_2 and HCO_3^-

Logistic regression												
Test	G1 & GC				G4 & GC				G3 & G4			
	pH	pCO_2	pO_2	HCO_3^-	pH	pCO_2	pO_2	HCO_3^-	pH	pCO_2	pO_2	HCO_3^-
Estimate	11,91	0,026	0,025	0,909	0,94	0,67	2,96	1,03	6,5E+01	6E+01	0,17	1,5E+0
OR (unit ch)	141312	1,026	1,026	0,402	0,39	0,51	19,5	2,8			1,18	4,4E+0
OR (range)	12,95	1,619	4,109	0,013	0,65	0,01		366	4,5E+10	5E+10	218	4,5E+0,5

CONCLUSION

Acid-base balance indicators obviously cannot be considered as unconditional markers of carcinogenesis, but their monitoring and, in particular, venous blood pH, of patients after special treatment, can help determine the risk group of patients who may develop of a malignant neoplasm recurrence.

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