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ASSOCIATION BETWEEN HYPOXIA LEVEL IN GASTRIC CANCER, ASSESSED BY ^{31}P NMR SPECTROSCOPY, AND RESULTS OF PATIENTS TREATMENT WITH DIFFERENT METHODS

Aim: *to analyse the association between gastric cancer hypoxia level and results of patients treatment.* ***Patients and methods:*** *the specimens of primary gastric cancer were investigated. 150 naïve patients were enrolled into the study. Tumor hypoxia level was assessed by ^{31}P NMR spectroscopy in perchloric extracts of tumor obtained after surgical excision. Patients were treated by operation alone, neoadjuvant or adjuvant chemotherapy in accordance with standards of therapy.* ***Results:*** *it was determined that hypoxia of primary tumor decreases the efficacy of neoadjuvant as well as adjuvant chemotherapy. It was revealed that negative influence of regional lymph node metastases on the disease outcome is enhanced by tumor hypoxia. It was shown that the risk of unfavorable disease outcome in patients with N_0 category and tumor characterized by severe hypoxia is significantly increased.* ***Conclusions:*** *negative influence of tumor hypoxia on neoplasia response to cytostatic chemotherapy was confirmed; the evidences for the expediency of the evaluation of hypoxia level in gastric cancer in biopsy and/or operation specimens before the choice of therapy methods were obtained.*

INTRODUCTION

Problem of effective treatment of patients with gastrointestinal malignancies, in particular gastric cancer still needs a radical solution. Despite of some success in combined therapy of these patients including new surgical technologies, target therapy and modern radiation treatment, outcome results are not improved [1, 2]. One of the promising approaches directing to enhance the antitumor therapy efficacy there are investigations aimed to evaluate the molecular profile of tumor for each patient for individualized therapy [3, 4]. Tumor hypoxia, i.e., low level of oxygenation, stipulated by defective anatomy and physiology of tumor vascularity, occupies a special place among biological features of malignant neoplasia [5, 6]. Hypoxia is considered as a key factor in tumor pathogenesis and malignant progression. Obtained experimental and clinical evidences have shown that hypoxic fraction of solid tumors stimulates the growth and metastatic potential, and reduces the sensitivity to radiation as well to the number of cytostatics [7–10]. In several studies it was demonstrated that low value of partial pressure of oxygen (pO_2), i.e., high level of hypoxia and overexpression of hypoxia-associated proteins in tumor may predict the unfavorable disease outcome [11, 12]. Results of clinical observations have allowed to recommend the use of hypoxia level in tumor and expression of hypoxia-associated proteins as prognostic factors [7, 11, 13–15].

Nuclear-magnetic resonance (NMR) spectroscopy, being a very convenient and informative technique *in vitro* and *in vivo* investigations has been widely applied.

NMR *in vivo* in combination with NMR-imaging has so far proven useful in differentiating malignant and benign tumors, permitting non-invasive detection and characterization of the tumors, monitoring of a number of relevant metabolites and in accordance with their changes to estimate the efficacy of applying therapy and prevent recurrence[16–18]. It is well known that metabolic ratios, obtained by NMR spectroscopy, are very informative in the assessment of tissue bioenergetic status and associated with hypoxia level that permits application some metabolic ratios to assess the hypoxia level in tissue [19, 20]. It has to be noted that clinical practice commonly deals with advanced tumors where PCr (phosphocreatin) and/or $_{\beta}$NTP (adenosintriphosphate) often drop to undetectable values. Hence, for the evaluation of the bioenergetic status and hypoxia level in tumor PME/Pi (phosphomonoesters/inorganic phosphate) metabolic ratio become very useful because phosphomonoesters are very sensitive to the level of oxygenation (a highly significant linear correlation ($p < 0.001$) was found between the mean tissue pO_2 and the respective PME/Pi ratio**)** [20].

The results of our previous investigations using ^{31}P NMR [13] with analysis and comparison with other methods and indices for the evaluation of hypoxia level [19, 20] permitted us to use the PME/Pi metabolic ratio for the assessment of the hypoxia level in gastric cancer tissue. It was determined that median value of the PME/Pi ratio for the gastric cancer tissue was 1.4 (range 0.8–5.32). Tumors are characterized as severe hypoxic if the PME/Pi < 1.4, whilst if the PME/Pi > 1.4 — satisfactory oxygenated.

The aim of this study was to evaluate the hypoxia level in tumor tissue of patients with gastric cancer using ^{31}P NMR spectroscopy and determine its association with patients survival according to the methods of therapy.

PATIENTS AND METHODS

A total of 150 patients with gastric cancer (GC) have been enrolled into the study. It was investigated patients, treated with operation alone or with chemotherapy according to the scheme FAP (fluorouracil, adriamycin, cisplatin) prior to surgery (neoadjuvant chemotherapy) or after (adjuvant chemotherapy). Doses of the drugs as well as the scheme of chemotherapy have been provided according to the standard treatment. Tissue samples were taken immediately after tumor excision and put into the liquid nitrogen for the following investigating.

Tumors were classified and staged according to the TNM system [21] and histological types of tumor were evaluated by WHO histological classification [22]. Clinicopathological characteristics of the patients with GC are presented in the Table 1. All patients were thoroughly informed about the study that was approved by the local ethics committee.

Table 1

Patients and tumor characteristics

Characteristics	Number of patients n (%)
Gender	
Male	87 (58.0)
Female	63 (42.0)
Age (years)	
Median	62
Range	(28–80)
Histological type	
Adenocarcinoma	119 (79.3)
Mucinous adenocarcinoma	10 (6.7)
Signet-ring cell carcinoma	13 (8.7)
Undifferentiated carcinoma	8 (5.3)
Tumor location	
Upper third	27 (18.0)
Middle third	38 (25.3)
Lower third	76 (50.7)
Total	9 (6.0)
Grade (G)	
1	2 (1.3)
2	29 (19.3)
3	76 (50.7)
4	43 (28.7)
UICC stage	
I	18 (12.0)
II	34 (22.6)
III	52 (34.7)
IV	46 (30.7)
T-classification	
1	2 (1.3)
2	25 (16.7)
3	85 (56.7)
4	38 (25.3)
Nodal involvement	
N_0	60 (40.0)
N_{1-2}	90 (60.0)
Distant metastasis	
M_0	130 (86.7)
M_1	20 (13.3)
Total	150 (100.0)

Assessment of the hypoxia level has been provided using ^{31}P NMR spectroscopy in tissue perchloric acid (PCA) extracts. (^{31}P NMR Bruker 400 MHz, Widebore Ultrashield, AV-400 Eelectronics, Germany, at 161.976 MHz). ^{31}P NMR spectra have been obtained in the NMR Spectroscopy Center (G.V. Kurdyumov Institute for Metal Physics, NAS of Ukraine).

As a standard, methylenediphosphonic acid, trisodium salt (Sigma, США) was used. All ^{31}P chemical shifts in the spectra were set relative to PCr by setting the PCr signal to 0.00 ppm. The areas of the signals on the ^{31}P NMR spectra were determined by the integration mode of the spectrometer. For the assessment of the hypoxia level in tumor of patients with GC it was used the ^{31}P PME/Pi metabolic ratio. All details of ^{31}P NMR method as well preparation of PCA tissue extracts have been presented in our earlier publication [13, 23].

All statistical analyses were conducted using the NCSS 2000/PASS 2000 and Prism, version 4.03 software packages. The survival proportion was estimated using the Kaplan — Meier method and differences in survival were analyzed with the log-rank test. Prognostic values of relevant variables were analysed by means of the Cox proportional hazards model using hazard ratio (HR) and χ^2 test. Two-tailed p values < 0.05 were considered statistically significant.

RESULTS AND DISCUSSION

The level of hypoxia was assessed in all patients using PME/Pi ratio that allowed to divide the patients into the two groups: patients whose tumors were in a state of severe hypoxia (PME/Pi <1.4) and in a state of satisfactory oxygenated (PME/Pi>1.4). It should be noted that the hypoxia level in GC was correlated neither with T, N or M categories (UICC classification) nor with stage of disease. This corresponds to well known fact that hypoxia level does not depend on tumor size, histological type, grade of differentiation, size of necrotic regions or clinical stage [7]. All patients were divided into groups in the following: first group included patients who received surgery alone, the second — adjuvant chemotherapy, and the third — neoadjuvant chemotherapy.

58 patients have been treated with operation alone, of these 25 patients (43.1%) died; 59 patients with adjuvant chemotherapy, of these 30 patients (50.8%) died; and 33 patients with neoadjuvant chemotherapy, of these 19 patients (57.6%) died. The death of all patients was related to GC.

31 patients who have been operated only had N_0 category, of these 12 (38.7%) died, and 27 patients — N_1 category, of these 14 (51.9%) died. Among patients who underwent operation followed by adjuvant chemotherapy 17 patients had N_0 category and 42 — N_1,category, of these 3 patients (17.6%) and 27 (64.3) died, respectively. Among patients who have been treated with neoadjuvant chemotherapy 13 patients had N_0, of these 4 patients (30.8%) died, and 20 patients had N_1, of these 15 (75%) died. These data clearly show the negative impact of the metastases in regional lymph nodes on the results of treatment and confirm their well-known prognostic significance [24, 25]. It should also be noted that the primary tumor hypoxia corrects the well known fact of negative im-

pact of regional metastasis on disease outcome. The analysis of influence of hypoxia level on prognosis of disease outcome has indicated that risk of dying was increased by a factor of more than 2.0 (hazard ratio 2,39; 95%CI 1,135–5,342; $\chi^2 = 5,204$; $p = 0,035$) for patients with N_0 category and when primary tumor was characterized by severe hypoxia. These data indicate, probably, the necessity to use adjuvant chemotherapy in patients with high level hypoxia even with "negative" lymph nodes, i.e., without diagnosed regional metastases. Unfavorable disease outcome in cervical cancer patients with negative lymph nodes and high level of hypoxia in primary tumor was observed by Fyles et al. [26].

In accordance with hypoxia level in the primary tumor in each group of patients it was detected as tumors characterized by severe hypoxia as well satisfactory oxygenation (Table 2). Data presented in Table 2 demonstrate almost homogenous distribution as a number of patients (%) as well according to hypoxia level in primary tumor in each group of patients. It allows to compare the survival in all groups of patients. It has to be noted that despite hypoxia level was evaluated in surgical specimens in patients who have been treated with neoadjuvant chemotherapy, i.e., chemotherapeutic drugs impact on tumor metabolism resulting in possible correction of hypoxic status, this group was analyzed to detect the influence just of cytostatic drugs on hypoxia level. Obtained results showed that hypoxic tumors after neoadjuvant chemotherapy were detected in 18 patients (54.5%), whereas satisfactory oxygenated — in 15 (45.5%) (see Table 2). Overall, 33 patients were in this group, of these 11 patients (61.1%) died with hypoxic tumors, and 8 (53.3%) with satisfactory oxygenated tumors. These data allow to suggest that neoadjuvant chemotherapy did not significant influence the indices that determine the hypoxia level.

Survival of GC patients in a accordance with N category and hypoxia level in primary tumor who have been treated with different methods was presented in Tables 3 and 4. The data of Table 3 demonstrate that treatment with neoadjuvant chemotherapy has not given the positive result, just as it was expected, in comparison with operation alone or adjuvant chemotherapy both for all patients and, especially, for those with hypoxic tumors. When surgical operation or chemotherapy was used for patients with satisfactory oxygenated primary tumors the more efficacy both neoadjuvant and adjuvant chemotherapy was observed, but the differences were statistically significant for adjuvant chemotherapy only ($p < 0.05$). Obtained results have confirmed the position concerning negative impact of hypoxia on tumor response to cytostatic therapy [7–9]. The results presented in Table 4 indicate that more favorable method for the patients with satisfactory oxygenated tumors and negative N status is a surgical operation. It should be noted that there were not enough number of patients with N_0 category who have been treated with neoadjuvant or treated with adjuvant chemotherapy. At the same time it is clearly seen that presence of metastases in regional lymph nodes is a reason to apply the adjuvant chemotherapy, although the significant effect after its applying was not observed, especially in patients with hypoxic tumors.

Table 2

Patient groups in accordance with tumor hypoxia level and therapy methods

PME/Pi ratio (hypoxia level)	Patient groups in accordance with therapy methods (n; %)		
	Operation	Adjuvant chemotherapy	Neoadjuvant chemotherapy
PME/Pi < 1.4 ("severe" hypoxia) (M±m, range)	1.05 ± 0.04 (0.6–1.35) (27; 46.6)	1.02 ± 0.05 (0.44–1.39) (32; 54.2)	1.02 ± 0.06 (0.6–1.4) (18; 54.5)
PME/Pi > 1.4 (satisfactory oxygenation) (M±m, range)	1.95 ± 0.1 (1.41–3.99) (31; 53.4)	1.99 ± 0.11 (1.43–3.79) (27; 45.8)	2.04 ± 0.2 (1.42–3.91) (15; 45.5)

Table 3

Survival of GC patients as a function of hypoxia level in primary tumor and different therapy methods (in months)

Therapy method	Overall survival, (M±m, range)	Hypoxia level, PME/Pi	
		< 1.4 (M±m, range)	> 1.4 (M±m, range)
Operation, n = 25	15.7 ± 1.86 (2.5–41.7) n = 25	15.5 ± 2.53 (2.5–29.6) n = 15	16.5 ± 2.8 (4.46–41.7) n = 10
Operation + adjuvant chemotherapy, n = 30	14.6 ± 1.56 (3.15–33.9) n = 30	11.6 ± 1.44 (3.15–20.6) n = 13	17.0 ± 2.4 (3.35–33.9) n = 17
Neoadjuvant chemotherapy + operation, n = 19	12.3 ± 1.76 (1.1–28.9) n = 19	11.1 ± 2.58 (1.1–27.3) n = 11	13.2 ± 2.33 (1.35–28.9) n = 8

Survival of GC patients was assessed by Kaplan — Meier method in accordance with hypoxia level in tumor (PME/Pi ratio) and method of treatment. Survival of patients who have been treated with operation alone or

Table 4

Survival of GC patients as a function of N category and hypoxia level in primary tumor as well as different therapy methods (in months)

Therapy method	Patients with N_0 category			Patients with N_{1-2} category		
	Overall survival (M±m, range)	Hypoxia level, PME/Pi		Overall survival (M±m, range)	Hypoxia level, PME/Pi	
		< 1.4 (M±m, range)	> 1.4 (M±m, range)		< 1.4 (M±m, range)	> 1.4 (M±m, range)
Operation, n = 25	19.0 ± 3.16 (2.5–41.7) n = 12	16.7 ± 4.6 (2.5–29.6) n = 7	22.2 ± 3.9 (11.9–41.7) n = 5	13.8 ± 1.84 (6.9–29.5) n = 13	9.9 ± 2.6 (6.9–20.6) n = 8	14.2 ± 1.03 (3.3–29.5) n = 5
Operation + adjuvant chemotherapy, n = 30	18.2 ± 5.3 (11.4–28.7) n = 3	12.9 ± 3.4 n = 2	28.7 n = 1	14.2 ± 1.64 (3.4–33.9) n = 27	11.3 ± 1.69 (3.4–20.6) n = 11	16.3 ± 2.43 (4.5–33.9) n = 16
Neoadjuvant chemotherapy + operation, n = 19	15.6 ± 5.4 (6.5–23.4) n = 4	13.1 ± 2.9 (6.5–19.9) n = 3	23.4 n = 1	11.6 ± 1.85 (1.1–27.3) n = 15	11.0 ± 2.5 (1.1–23.4) n = 8	13.5 ± 2.6 (1.36–27.3) n = 7

treated with adjuvant chemotherapy in accordance with hypoxia level have been compared (Fig. 1, 2).

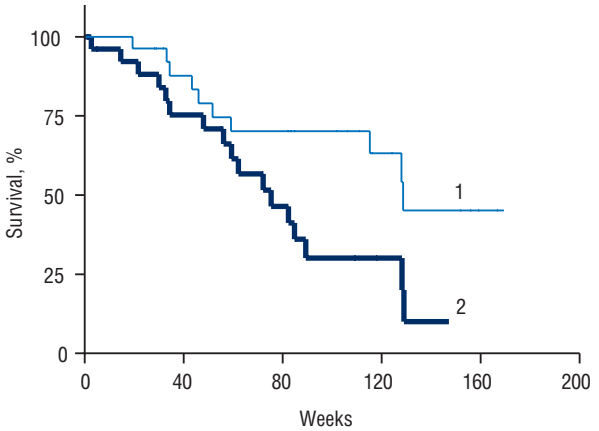

Fig. 1. Kaplan — Meier overall survival curves for GC patients as a function of PME/Pi ratio in tumor tissue (1 — PME/Pi > 1.4; 2 — PME/Pi < 1.4), log-rank test, $\chi^2 = 5.204$, $p = 0.0225$. Patients who have been operated only were analyzed

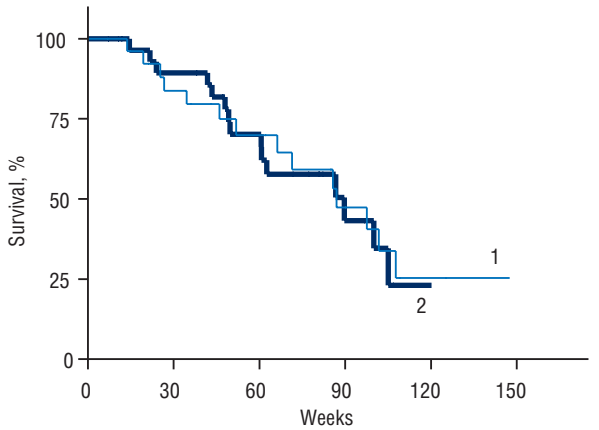

Fig. 2. Kaplan — Meier overall survival curves for GC patients as a function of PME/Pi ratio in tumor tissue (1 — PME/Pi > 1.4; 2 — PME/Pi < 1.4), log-rank test, $\chi^2 = 0.03441$, $p = 0.8533$. Patients who were treated with adjuvant chemotherapy were analysed

Obtained results have clearly shown inefficacy of surgical treatment alone of patients with hypoxic tumors: survival of these patients was poorer than those in patients with satisfactory oxygenated tumors (Fig. 1; $p = 0.0225$). There was not difference in survival of patients treated with adjuvant chemotherapy and having hypoxia tumors or having satisfactory oxygenated tumors (Fig. 2). Such situation conincides to certain extent with data of life-span of patients who had tumors with different level of oxygenation and were treated with adjuvant chemotherapy (see Table 3). At the same time it has to be noted that Kaplan — Meier method gives the possibility to analyse the actuarial survival only, whereas data in Table 3 represent actual survival and indicate the definite efficacy of adjuvant chemotherapy and expediency of its using. At the same time data on Fig. 3 that compare the survival of patients with hypoxic tumors only, demonstrate the absence of differences between survival of patients treated with operation alone and treated with adjuvant chemotherapy, that coincides with results presented in Table 3.

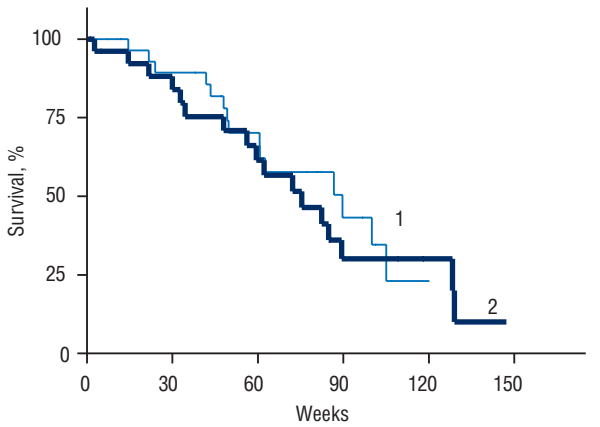

Fig. 3. Kaplan — Meier overall survival curves for GC patients as a function of therapy methods (1 — adjuvant chemotherapy; 2 — operation alone), log-rank test, $\chi^2 = 0.1959$, $p = 0.6580$. All patients were characterized by "hypoxic" tumors (PME/Pi ratio < 1.4)

Survival of patients with satisfactory oxygenated tumors was preferably after operation alone (Fig. 4). Such conclusion that is in a certain sense paradoxical, is somewhat disproved by the clinical characteristics of patients. Group of patients who were treated with adjuvant chemotherapy or operation alone were differed by stage of disease and N and M categories: the number of patients with stage III in group of adjuvant chemotherapy and in group of operation alone was 48.1% and 24%, in stage IV — 37% and 13%, with N_1 category — 86.2% and 31% and with M_1 category — 14.8% and 6.9%, respectively. These data explain the obtained results of therapy and emphasize both of complexity of GC treatment [24, 25], and negative effect of tumor hypoxia on chemotherapy efficacy (see Tables 3 and 4).

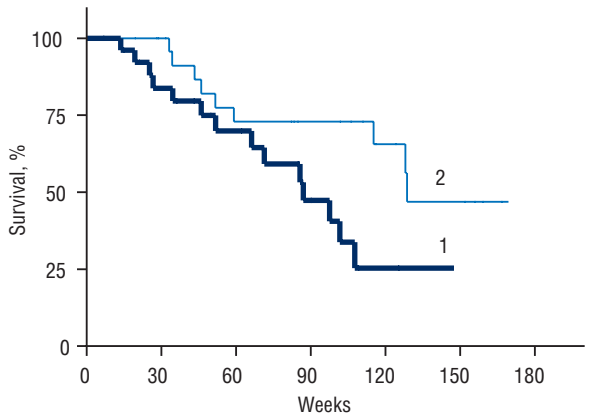

Fig. 4. Kaplan — Meier overall survival curves for GC patients as a function of therapy methods (1 — adjuvant chemotherapy; 2 — operation alone), log-rank test, $\chi^2 = 4.449$, $p = 0.0349$. All patients were characterized by "oxygenated" tumors (PME/Pi ratio > 1.4)

CONCLUSION

1. Hypoxia of primary tumor negatively influences the efficacy of different methods of treatment: surgical intervention alone as well neoadjuvant or adjuvant chemotherapy.

2. Negative impact of metastases in regional lymph nodes on disease outcome is significantly enhanced by hypoxia of primary tumor.

3. Obtained results give the reason to consider expedient the application of the adjuvant chemotherapy in patients with hypoxic tumors, probably, in the early stages of disease, even for patients with negative lymph node status.

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ЗВ'ЯЗОК МІЖ РІВНЕМ ГІПОКСІЇ ТКАНИНИ РАКУ ШЛУНКА ТА РЕЗУЛЬТАТАМИ ЛІКУВАННЯ ХВОРИХ РІЗНИМИ МЕТОДАМИ

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Резюме. ***Мета:*** *проаналізувати зв'язок між рівнем гіпоксії тканини раку шлунка (РШ) та результатами лікування хворих.* ***Методи:*** *у дослідження включено 150 хворих на первинний РШ, яким проведено лише оперативне лікування або застосовано неоад'ювантну чи ад'ювантну хіміотерапію (ХТ) відповідно до стандартів. Рівень гіпоксії визначали методом ^{31}P ядерної магнітно-резонансної спектроскопії перхлорних екстрактів пухлини, отриманої відразу після видалення, оцінюючи метаболічне співвідношення PME/Pi.* ***Результати:*** *встановлено, що гіпоксія первинної пухлини (PME/Pi < 1,4) негативно впливає на ефективність як самої лише операції, так і неоад'ювантної чи ад'ювантної ХТ. Визначено, що негативний вплив регіонарних метастазів (N_1) на перебіг захворювання підсилюється гіпоксією пухлини. У хворих із категорією N_0 за умов гіпоксії пухлини ризик несприятливого перебігу захворювання також зростає.* ***Висновки:*** *підтверджено негативний вплив гіпоксії пухлини на відповідь останньої на цитостатичну ХТ; отримано докази доцільності визначення рівня гіпоксії РШ в операційному матеріалі для вибору методу лікування.*

Ключові слова: рак шлунка, гіпоксія, ЯМР-спектроскопія, хіміотерапія.

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