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RESULTS OF USING ADJUVANT PERFUSION CHEMOTHERAPY IN RADICAL TREATMENT OF INFILTRATIVE GASTRIC CANCER

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ABSTRACT

Relevance: *Given the high biological aggressiveness of infiltrative gastric cancer warranting a need for a multimodal approach to its radical treatment employing adjuvant perfusion thermochemotherapy (HIPEC) and systemic adjuvant polychemotherapy, the goal of the present study was to assess the efficacy and expediency of such an approach.*

The study aimed to *evaluate the effectiveness of a combination of HIPEC and systemic adjuvant polychemotherapy in patients radically operated on for infiltrative forms of gastric cancer pT4a-bN0-3M0.*

Methods: *The study examined the long-term results of radical treatment for gastric cancer in 141 patients (pT4a-bN0-3M0, Borrmann type III-IV).*

Of them, 18 patients underwent a multimodal treatment, including radical surgery in combination with HIPEC and systemic adjuvant polychemotherapy (ACT) (oxaliplatin 100 mg/m² (on day 1 of the cycle), capecitabine 1.000 mg/m² or tegafur 10-15 mg/kg (2 times per day, on days 1-14 of the cycle, with a 7-day break between cycles, 8 cycles) – HIPEC/ACT group. For comparison purposes, we used the data on 55 radically operated patients (surgery control) and 68 other patients who underwent radical surgery in combination with HIPEC (cisplatin 50 mg/m² + doxorubicin 50 mg/m², 42⁰C, one hour). The long-term treatment results were evaluated using competing risks analysis, the Kaplan-Meier multiplier method, and multivariate analysis (Cox and Fine-Gray models).

Results: *The multimodal treatment group showed a decrease in unfavorable outcomes associated with tumor progression (β = -2.14, RR 0.12, 95% CI 0.04-0.38, p<0.001), a decrease in the risk of carcinomatosis (β=-1.99, RR 0.14, 95% CI 0.04-0.44, p<0.001), and better five-year survival rates compared to the control groups. The adjusted survival was 81.9±9.5% (p=0.003), the progression-free survival was 82.2±9.3% (p<0.001), and the dissemination-free survival was 81.9±9.5% (p<0.001).*

Conclusion: *It is advisable to supplement the standard approach for infiltrative gastric cancer (radical surgery and systemic polychemotherapy) with perfusion HIPEC to prolong the remission of the tumor process.*

Keywords: *gastric cancer, adjuvant hyperthermic intraperitoneal chemotherapy (AHIPEC), adjuvant systemic polychemotherapy (ACT).*

Introduction: High invasive and metastatic potential of infiltrative forms of gastric cancer (GC) causes early progression of the tumor process even in radically operated patients [1]. The latter determines the necessity of complex treatment to prevent the development of various variants of cancer progression, both implantation metastases and systemic progression in the form of lymphohematogenous metastasis. The current strategy of radical treatment of locally advanced cancer involves the use of perioperative or adjuvant polychemotherapy (APChT) [2, 3], which cannot prevent the development of metachronous peritoneal dissemination (MPD) due to insufficient effective penetration of chemotherapy from the systemic blood flow into the peritoneal tissue due to the presence of hematoperitoneal barrier. Several recent publications emphasize the excellent use of adjuvant perfusion thermochemotherapy (APTChT) for this purpose [4]. It is also noted the necessity of its combination with APChT to prevent the systemic progression of GC [5-7].

The study aimed to evaluate the effectiveness of a combination of HIPEC and systemic adjuvant polychemotherapy in patients radically operated on for infiltrative forms of gastric cancer pT4a-bN0-3M0.

Materials and methods: The study was conducted at the Republican Scientific and Practical Center of Oncology and Medical Radiology, named after N.N. Aleksandrov, in 2008-2021. Data on the treatment results of 141 patients radically operated for GC stage IIB-IIIC (type III-IV according to Borrmann, 1926) were used to prepare this article. In 18 patients, a previously developed comprehensive approach to treatment [5-7], which included, in addition to radical surgery, a combination of APTChT (cisplatin, doxorubicin, 42⁰C, 1 hour) in combination with 7-8 courses of APChT (oxaliplatin, capecitabine or tegafur) – APTChT+APChT group – was

used. We used data from patients included in a previously conducted prospective randomized trial [8] for a comparative evaluation of the effect of this comprehensive approach on the progression pattern and survival rates, in which two groups were formed: 1) the APTChT group (68 people, including 42 men, 26 women; mean age, 56±8 years) – APTChT was used in treatment in addition to radical surgery in the mode presented above; 2) the surgical control (SC) group (55 people, including 34 men, 21 women; mean age, 56±9 years) (Table 1). Adjuvant therapy in the comparison groups was not performed according to the standards of GC treatment valid in the Republic of Belarus at the time of the prospective randomized study.

Table 1 - Characteristics of the study patients

Sign	SC group, n=55 (%)	APTChT group, n=68 (%)	APTChT + APChT group, n=18 (%)	p
Age (years), mean±SD	56.0±10.0	56.0±8.0	56.0±8.0	0.951
Gender				0.725
Male	34 (61.8)	42 (61.8)	13 (72.2)	
Female	21 (38.2)	26 (38.2)	5 (27.8)	
pT				0.626
pT4a	48 (87.3)	55 (80.9)	15 (83.3)	
pT4b	7 (12.7)	13 (19.1)	3 (16.7)	
pN				0.576
pN0	14 (25.5)	23 (33.8)	7 (38.9)	
pN1	6 (10.8)	8 (11.8)	3 (16.6)	
pN2	14 (25.5)	15 (22.1)	1 (5.6)	
pN3	21 (38.2)	22 (32.3)	7 (38.9)	
G				0.139
GI	4 (7.3)	6 (8.8)	1 (5.6)	
GII	9 (16.4)	17 (25)	4 (22.2)	
GIII	29 (52.7)	39 (57.4)	13 (72.2)	
GIV	13 (23.6)	6 (8.8)	0	

Note: SD – standard deviation

We assessed the following to evaluate the long-term results of treatment: adjusted survival (the event of death from the cause related to GC); progression-free survival (the event of registration of GC progression and death from the cause related to GC); dissemination-free survival (the event of registration of tumor dissemination through peritoneum and death from the cause related to GC were taken as the event of calculation).

The Kaplan-Meier multiplier method with the calculation of the standard error (SE) using the Greenwood formula was used to estimate survival rates. Surveillance was coded as "complete" if event data were available, and if no event information was available, as "censored." Competing risk analysis was used to analyze the pattern of progression, assessing the cumulative incidence (CI) of GC progression with the development of a) MPD; b) distant lymphohematogenous metastases (DLHM). Cumulative incidence was understood as an intensive index, reflecting the accumulation of the events considered over a specific time interval in the observation dynamics. The following events were considered when assessing the CI of GC progression variants: for MPD - the occurrence of progression with the development of carcinomatosis regardless of other progression variants if they were established simultaneously; for DLHM - cases of any progression in the absence of signs of carcinomatosis.

Comparing CIs of progression variants for two groups was performed using the Grey criterion [9]. The Fine-Gray model was used to determine unfavorable prognosis factors of metachronous peritoneal dissemination [10]. A nonparametric Cox proportional hazards model [11] was used to assess the effect of the used treatment option and tumor process characteristics on survival rate. The Bonferroni multiple-comparison correction was taken into account in paired comparisons.

Statistical analysis of the data was performed using the RV statistical package. 3.1.1 (GPL license) using *survival* [12] and *cmprsk* [13] packages.

Results: The median follow-up in the APTChT+APChT group was 84 months, and 104 months in the comparison groups.

The tendency to the improvement of long-term results of treatment in the most prognostically unfavorable cohort of patients noted during the interim evaluation of the results of this study [5, 6, 7] remained despite the increase of several patients in APTChT + APChT group and increase of follow-up period. In particular, the integrated treatment approach used reduced both the total number of cases of cancer progression and the incidence of MPD, which in the APTChT + APChT, APTChT, and SC groups were: the rate of progression – 16.7%; 55.9%, 87.3% (p<0.001); 2) the rate

of MPD – 0%; 23.5%; 78.2% (p<0.001), respectively. In addition, there were no cases of MPD and metachronous metastases in the liver in the APTChT+APChT group, the most frequent progression variants in the two comparison groups during the follow-up period.

The above demonstrated a change in the GC progression structure against the background of APTChT and APChT, manifested by a significant reduction in MPD frequency. These changes led, in turn, to changes in the cumulative incidence of the considered variants of cancer progression: there were no MPD cases (KI of this variant of progression – 0), and cumulative incidence of DLHM was comparable with the GC group and statistically significantly lower in comparison with the APTChT group (Table 2).

Table 2 – Five-year cumulative incidence of gastric cancer progression variants

Cumulative incidence (CI)	Patient group/Value of cumulative incidence (%±SE)			p_{Gray}
	APTChT + APChT	APTChT	SC	
CI of peritoneal dissemination*	0	23.6±5.2	75.1±6.1	<0.001
CI of DLHM**	17.1 ±9.3	28.0±5.5	5.5±3.1	0.007

Notes:
** - the onset of progression with the development of MPD independent of the other progression variant, if they were established at the same time, was considered as an event;*
*** - any progression in the absence of MPD signs was considered an event.*

Reduced incidence and CI of GC progression, including the development of MPD, when using APTChT+APChT combination in radically operated patients resulted in increased 5-year survival rate: In the APTChT+APChT, APTChT, and SC groups: 1) adjusted survival – 81.9±9.5%; 45.1±6.4%; 30.5±6.4%, respectively (p=0.003); 2) progression-free survival – 82.2±9.3%; 43.7±6.3%; 18.2±5.2%, respectively (p<0.001); 3) dissemination-free survival – 81.9±9.5%; 45.2±6.3%; 21.3±5.6%, respectively (p<0.001).

A multivariate analysis using the following prognostic models was performed to determine the combined effect of many factors determining both the local spread of the tumor process (pN) and the amount of antitumor treatment performed on the clinical course of GC in the long term after undergoing radical treatment:

Cox model - to assess risk factors for the onset of an adverse outcome due to GC progression (Table 3);

Fine & Gray model – to determine the risk factors of MPD as the most frequent and prognostically unfavorable variant of infiltrative GC progression (in comparison with DLHM) (Table 4).

Table 3 – Estimation of the relative risk of an adverse outcome associated with GC progression (Cox model)

Factors associated with adverse outcome	Results of regression analysis		
	β	RR (95% CI)*	p
pN1-2 *versus* pN0	0.84	2.3 (1.3-4.3)	0.007
pN3 *versus* pN0	1.58	4.8 (2.6-9)	<0.001
Type of surgery: Standard or combined gastrectomy *versus* Subtotal gastric resection	0.57	1.8 (1.1-2.8)	0.018
Surgical treatment + APTChT *versus* Surgical treatment	-0.76	0.47 (0.3-0.72)	<0.001
Surgical treatment + APTChT + APChT *versus* Surgical treatment	-2.14	0.12 (0.04-0.38)	<0.001

Notes: RR - relative risk; CI - confidence interval

Table 4 - Assessment of relative risk of progression with development of metachronous peritoneal dissemination (Fine & Gray model)

Factors associated with the development of metachronous peritoneal dissemination	Results of regression analysis		
	β	RR (95% CI)*	p
pN1-2 *versus* pN0	0.84	2.3 (1.2-4.4)	0.009
pN3 *versus* pN0	1.48	4.4 (2.3-8.2)	<0.001
Type of surgery: Standard or combined gastrectomy *versus* Subtotal gastric resection	0.51	1.7 (1.03-2.7)	0.039
Surgical treatment + APTChT *versus* Surgical treatment	-0.65	0.52 (0.34- 0.81)	0.004
Surgical treatment + APTChT + APChT *versus* Surgical treatment	-1.99	0.14 (0.04-0.44)	<0.001

Notes: RR - relative risk; CI - confidence interval

Several well-known predictors of the adverse clinical course of GC, used in this study as inclusion criteria, were not included in the model: a) macroscopic growth form – Borrmann type III-IV; b) tumor invasion of serous gastric membrane or tumor transition to adjacent structures – pT4a-b.

It was found that the risk factors of adverse outcomes due to GC progression (Cox's model, Table 3) and the development of metachronous peritoneal dissemination (Fine & Gray model, Table 4) were:

1. Metastatic involvement of regional lymph nodes - an increase in the risk of adverse outcomes associated with GC progression and the risk of MPD development was noted in parallel with an increase in the degree of metastatic involvement of regional lymph nodes. It was previously noted when evaluating the interim results of this study [5, 6, 7] and is consistent with the literature [14].

2. Necessity of gastrectomy in standard or combined variant due to more extended tumorous process (compared to subtotal gastric resection).

The use of APTChT in an isolated variant and combined with systemic APChT reduced the risk of adverse outcomes associated with GC progression and the risk of MPD, which had been previously noted in the previous stages of the study [7]. However, it is noteworthy that the achieved effect was maintained despite an increase in the follow-up median.

The latter emphasizes the importance of APTChT (or intraperitoneal chemotherapy in any known variants) in the complex treatment of patients radically operated on for infiltrative GC. This helps prevent the most prognostically unfavorable variant of GC progression, such as metachronous peritoneal dissemination.

Discussion: The presented results of our studies demonstrate the necessity and appropriateness of APTChT as a compulsory component of the complex treatment of infiltrative forms of GC, which does not contradict modern standards of radical treatment of this pathology, involving in addition to surgical treatment of the use of one of the options of systemic chemotherapy, perioperative or adjuvant.

It was previously noted that the undoubted advantage of combining intraperitoneal and systemic chemotherapy in radically operated for infiltrative forms of GC is the simultaneous prevention of various options of GC progression: a) metachronous peritoneal dissemination due to elimination of free tumor cells from the peritoneal cavity by APTChT; b) systemic progression of GC by APChT [1, 5, 15, 16]. The results demonstrated above emphasize the adequacy of such an approach to improve the long-term results of treatment of this category of patients, as well as demonstrate long-term remission of tumor process in patients of the prognostically unfavorable category (infiltrative cancer, metastatic lesion of regional lymph collection, invasion of serous lining of the stomach).

A differentiated approach to the definition of antitumor treatment based on individual assessment of the probability of metachronous peritoneal dissemination using prognostic models is a promising way to improve the results of locally disseminated GC treatment. The latter will allow supplementing the standard volume of treatment measures with perfusion thermochemotherapy exactly in patients with an objectively established high risk of MPD development, thus preventing excessive treatment in patients with low (or standard risk) of the considered variant of progression and avoiding undesirable complications associated with the unreasonable performance of APTChT and APChT [1, 4, 15, 16].

Conclusion: Using a combination of systemic APChT and APTChT is reasonable to increase the remission period of the tumor process in the radical treatment of infiltrative forms of pT4a-bN0-3M0 GC.

Complementing radical surgical treatment with perfusion thermochemotherapy (cisplatin, doxorubicin, at 42°C, 1 hour) and 7-8 courses of adjuvant polychemotherapy (oxaliplatin combined with capecitabine or tegafur) reduces the risk of metachronous peritoneal dissemination (β=-0.65, RR 0.52, 95% CI 0.34-0.81, p=0.004) and the risk of gastric cancer progression in either variant (β=-0.76, RR 0.47, 95% CI 0.3-0.72, p<0.001). This improves the survival of prognostically unfavorable patients.

The development of prognostic models allows estimating the risk of metachronous peritoneal dissemination for an individual approach to determining the volume of radical treatment of locally advanced gastric cancer, including its infiltrative forms, which seems actual.

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АҢДАТПА

АСҚАЗАН ОБЫРЫНЫҢ ИНФИЛЬТРАТИВТІ ТҮРЛЕРІН ТҮБЕГЕЙЛІ ЕМДЕУДЕ АДЪЮВАНТТЫ ПЕРФУЗИЯЛЫҚ ТЕРМОХИМИОТЕРАПИЯНЫ ҚОЛДАНУ НӘТИЖЕЛЕРІ

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Өзектілігі: *асқазан қатерлі ісігінің инфильтративті түрлерінің жоғары биологиялық агрессивтілігі адъювантты перфузиялық термохимиотерапия мен жүйелік адъювантты полихимиотерапияны қолдана отырып, оларды түбегейлі емдеуде кешенді тәсіл ретінде қажет етіледі.*

Зерттеудің мақсаты *– pT4a-bN0-3M0 асқазан қатерлі ісігінің инфильтративті түрлеріне түбегейлі операция жасалған емделушілерде адъювантты полихимиотерапия мен жүйелік адъювантты перфузиялық термохимиотерапия комбинациясының тиімділігін бағалау.*

Әдістері: *Асқазан қатерлі ісігіне байланысты түбегейлі операция жасалған 141 пациенттің (pt4a-bN0-3M0, R. Bormann бойынша III-IV тип) емдеу нәтижелеріне талдау жүргізілді, олардың 18-не адъювантты перфузиялық термохимиотерапиямен және жүйелік адъювантты перфузиялық термохимиотерапиямен түбегейлі операцияның комбинациясын қамтитын кешенді емдеу жүргізілді (оксалиплатин 100 мг/м² (1 күн курс), капецитабин 1000 мг/м² немесе тегафур 10-15 мг/кг (тәулігіне 2 рет, курстың 1-14 күні), үзіліс 7 күн, 8 курс)) – адъювантты перфузиялық термохимиотерапия+ адъювантты перфузиялық термохимиотерапия тобы. Салыстыру топтары ретінде 55 түбегейлі хирургиялық пациенттің (хирургиялық бақылау) деректері, сондай-ақ түбегейлі операция адъювантты перфузиялық термохимиотерапиямен толықтырылған 68 пациенттің деректері пайдаланылды (цисплатин 50 мг/м² + доксорубицин 50 мг/м², 42°С, 1 сағат) - адъювантты перфузиялық термохимиотерапия тобы. Ұзақ мерзімді емдеу нәтижелерін бағалау үшін бәсекелес тәуекелдерді талдау, Каплан-Мейерді көбейту әдісі, көп факторлы талдау (Кокс моделі, Файн-Грей моделі) қолданылды.*

Нәтижелері: *кешенді емдеу тобында ісік процесінің өршуіне байланысты қолайсыз нәтиженің туындау қаупінің төмендеуі байқалды – β= -2,14; ор 0,12 (95% сі 0,04-0,38), p<0,001, сондай – ақ канцероматоздың даму қаупі – β= -1,99; ОР 0,14 (95% сі 0,04-0,44), p<0,001; 5 жылдық өмір сүру деңгейінің жоғарылауы (бақылау топтарымен салыстырғанда): түзетілген – 81,9±9,5% (p=0,003); прогрессиясыз өмір сүру – 82,2±9,3% (p<0,001); таралудан бос өмір сүру – 81,9±9,5% (p<0,001).*

Қорытынды: *асқазан қатерлі ісігінің инфильтративті түрлерін түбегейлі хирургиялық емдеуден кейін ісік процесінің ремиссия мерзімін ұзарту үшін перфузиялық интраоперациялық интраперитонеальді термохимиотерапия жүргізу арқылы стандартты тәсілді (жүйелік полихимиотерапиямен біріктірілген операция) толықтыру орынды.*

Түйінді сөздер: *асқазан қатерлі ісігі, адъювантты перфузиялық термохимиотерапия (АПТХТ), адъювантты жүйелік полихимиотерапия (АЖПХТ).*

АННОТАЦИЯ

РЕЗУЛЬТАТЫ ПРИМЕНЕНИЯ АДЪЮВАНТНОЙ ПЕРФУЗИОННОЙ ТЕРМОХИМИОТЕРАПИИ ПРИ РАДИКАЛЬНОМ ЛЕЧЕНИИ ИНФИЛЬТРАТИВНЫХ ФОРМ РАКА ЖЕЛУДКА

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Актуальность: *Высокая биологическая агрессивность инфильтративных форм рака желудка диктует необходимость комплексного подхода к их радикальному лечению с применением адъювантной перфузионной термохимиотерапии (АПТХТ) и системной адъювантной полихимиотерапии (АПХТ).*

Цель исследования *– оценить эффективность комбинации АПТХТ и системной АПХТ у пациентов, радикально оперированных по поводу инфильтративных форм рака желудка pT4a-bN0-3M0.*

Методы: *Проведен анализ результатов лечения 141 радикально оперированного по поводу РЖ (pT4a-bN0-3M0, III-IV тип по R.Bormann) пациента, у 18 из которых было проведено комплексное лечение, включающее комбинацию радикальной операции с АПТХТ и системной АПХТ (оксалиплатин 100 мг/м^2 (1 день курса), капецитабин 1000 мг/м^2 или тегафур 10-15 мг/кг (2 раза/сутки, 1-14 день курса), перерыв 7 дней, 8 курсов)) – группа АПТХТ+АПХТ. В качестве групп сравнения использовали данные 55 радикально оперированных пациентов (хирургический контроль), а также 68 пациентов, у которых радикальная операция была дополнена АПТХТ (цисплатин 50 мг/м^2 + доксорубицин 50 мг/м^2, 42^{0}С, 1 час) – группа АПТХТ. Для оценки отдаленных результатов лечения использованы анализ конкурирующих рисков, метод множительных оценок Каплана-Мейера, многофакторный анализ (модель Кокса, модель Файна-Грея).*

Результаты: *В группе комплексного лечения отмечено снижение риска наступления неблагоприятного исхода, связанного с прогрессированием опухолевого процесса – β= -2,14; ОР 0,12 (95% ДИ 0,04-0,38), p<0,001, а также риска развития канцероматоза – β= -1,99; ОР 0,14 (95% ДИ 0,04-0,44), p<0,001; увеличение показателей 5-летней выживаемости (в сравнении с группами контроля): скорректированной – 81,9±9,5% (p=0,003); выживаемости, свободной от прогрессирования – 82,2±9,3% (p<0,001); выживаемости, свободной от диссеминации – 81,9±9,5% (p<0,001).*

Заключение: *Для увеличения сроков ремиссии опухолевого процесса после радикального хирургического лечения инфильтративных форм рака желудка целесообразно дополнение стандартного подхода (операция в сочетании с системной полихимиотерапией) проведением перфузионной интраоперационной интраперитонеальной термохимиотерапии.*

Ключевые слова: *рак желудка, адъювантная перфузионная термохимиотерапия (АПТХТ), адъювантная системная полихимиотерапия (АПХТ).*

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