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Intraoperative risk assessment of carcinomatosis development after radical surgery for gastric cancer

Relevance: *Metachronous peritoneal dissemination (PD) is the most frequent pattern of gastric cancer (GC) progression after radical surgery. It is necessary to take into account the existing risk of developing metachronous PD to ensure a substantiated administration of intraperitoneal chemotherapy (ICT) for its timely prevention.*

The purpose of the study *was to raise the metachronous PD prognostication efficacy.*

Results: *The treatment outcomes of 1,065 radically operated patients (males – 640, 60.1%; females – 425, 39.9%) aged 23 to 89 years (median age – 63±12) showed that a high risk of GC recurrence in the form of peritoneal dissemination is associated with: (1) metastatic invasion of the regional lymph node – pN2-3 – RR 2.0 (95% CI 1.5–2.7), p < 0.001; (2) ulcero-infiltrative and diffuse infiltrative forms of primary gastric cancer growth – RR 3.7 (95% CI 2.5–5.5), p < 0,001), and RR 2.3 (95% CI 1.5–3.6), p<0,001; (3) serosa invasion by primary GC (pT4) – RR 2.5 (95% CI 1.8–3.6), p<0,001; (4) combined surgical treatment vs. standard surgery – RR 1.8 (95% CI 1.2–2.7), p=0.005; and (5) performing gastrectomy vs. distal resection – RR 1.6 (95% CI 1.2–2.2), p=0.004.*

A multivariate analysis (Fine-Grey model) was done to propose a prognostic model for an intraoperative estimate of the MPD development probability to determine indications for intraoperative ICT (concordance index – 0.75).

Conclusion: *The proposed nomogram- or formula-based prognostic model allows a differentiated approach to administering intraoperative ICT, taking into account the existing probability of peritoneal dissemination development.*

Keywords: *gastric cancer (GC), peritoneal dissemination (PD).*

Introduction: Peritoneal dissemination (PD) is one of the main ways of progression of gastric cancer (GC) after radical surgery. PD answers for 40-60% of progression cases [1, 2]. Intraperitoneal chemotherapy (ICT) is usually used to prevent PD. Therefore, intraoperative ICT has been proposed to ensure the most complete contact of the cytostatic with the peritoneum surface [3]. Besides, the stratification of patients based on the risk of developing PD seems appropriate to increase ICT effectiveness. Such risk can be assessed using prognostic models.

The purpose of the study was to raise the metachronous PD prognostication efficacy.

Material and methods: The study was based on the analysis of long-term treatment outcomes in 1,065 patients who underwent radical surgery at N.N. Alexandrov National Cancer Centre of Belarus in 2008–2016. Of them, 640 (60.1%) were male and 425 (39.9%) female. The age of patients varied from 23 to 89 years, with an average age of 63±12 years. The patients received no adjuvant or neoadjuvant treatment.

The tumor process spread level is provided in Table 1.

Table 1 – The tumor process spread level, pTN

Tumor inva-sion depth	Degree of metastatic lesion of the regional lymph collector, pN				No. of pa-tients
	pN0	pN1	pN2	pN3	
pT1	204	22	5	0	231
pT2	146	44	12	4	206
pT3	78	44	30	13	165
pT4	153	95	86	129	463
Total patients	581	205	133	146	1065

Histologically, all patients had adenocarcinomas of various differentiation degree: GI – 114 patients, GII – 352, GIII – 518, GIV – 81. The forms of tumor growth by Borrmann were mainly infiltrative: the diffuse-infiltrative and ulcerative-infiltrative (253 and 329 cases, respectively), as well as saucer-like (451), and polypoid (32).

The analysis of competing risks was used in assessing the long-term treatment outcomes [4]. The considered competing events included: 1) cases of GC progression with PD (every progression with PD independent from the other variant of progression was counted if they were detected simultaneously); 2) the cases of CG progression with the development of distant lymphohematogenous metastases (DLHM) – any progression in the absence of signs of carcinomatosis was counted. Cumulative incidence (CI) of events was assessed; the incidence for different groups was compared using the Gray criterion [5]. The Fine and Gray model was used for multivariate analy-

sis [6]. Confidence intervals (CIs) of relative risk (RR) were calculated based on the corresponding CI of regression coefficients. Statistical analysis of data was performed using the statistical package R v. 3.1.1, the *survival* [7] and *cmprsk* [8] modules.

Results and Discussion: The median follow-up was 48 months, the median time to progression with PD – 10.1 months, with DLHM – 13.4 months. The assessment of the effect of clinical and morphological characteristics of the tumor process and the volume of treatment on the 4-year CI of metachronous PD demonstrated its prevalence in:

1) ulcerative-infiltrative and diffuse-infiltrative GC – 22.6±0.09% and 38.1±0.08%, respectively, to compare the CI of dissemination in polypoid cancer 4.5±0.2%, in saucer-like – 7.7±0.02% (p < 0.001);

2) an increase in the depth of the primary tumor invasion into the stomach serous membrane: pT1 – 0.4±0.002%, pT2 – 4.6±0.02%, pT3 – 23.6±0.13%, pT4 – 36.0±0.06% (p<0.001);

3) an increase in the degree of metastatic lesion of the regional lymphatic collector: pN0 – 9.6±0.02%, pN1 – 20.1±0.09%, pN2 – 32.7±0.2%, pN3 – 49.7±0.2% (p<0.001);

4) a decrease in the primary tumor differentiation degree: GI – 6.9±0.07%, GII – 15.9±0.04%, GIII – 22.3±0.04%, GIV – 41.4±0.33% (p<0.001);

5) combined operations (41.1±0.3%) vs. standard radical gastrectomy (27.3±0.07%), or subtotal gastrectomy (13.3±0.02%) – p<0.001;

6) the case of D2 lymph dissection (21.4±0.02%) vs. D1 (13.3±0.08) (p=0.034), which is explained by an increase in the number of free tumor cells in the abdominal cavity after D2 lymph dissection [9].

The patient age (in the age groups of 23-55, 56-65, 66-75, and above 75 years) or gender did not affect the GC progression.

A simultaneous influence of the above factors on the risk of developing a metachronous PD was evaluated in a multivariate analysis using the Fine-Gray competing risk model (Table 2).

Table 2 – Relative risk of developing metachronous PD

Adverse outcome factors	Regression analysis results				
	Preliminary model		Final model		
	β	p	β	PR (95% CI)	p
Age	0	0.15	–	–	–
Gender male vs. female	-0.11	0.48	–	–	–
Adenocarcinoma GII vs. GI	0.06	0.88	–	–	–
Adenocarcinoma GIII vs. GI	-0.02	0.32	–	–	–
Adenocarcinoma GIV vs. GI	0.52	0.96	–	–	–
Diffuse-infiltrative vs. saucer-like + polypoid	0.75	0.001	0.90	2.4 (1.6–3.8)	<0.001
Ulcer-infiltrative vs. saucer-like + polypoid	1.20	<0.001	1.25	3.5 (2.4–5.1)	<0.001
pN1 vs. pN0	0.38	0.08	0.35	1.4 (0.9–2.2)	0.092
pN2 vs. pN0	0.48	0.02	0.47	1.6 (1.0–2.4)	0.030
pN3 vs. pN0	0.94	<0.001	0.96	2.6 (1.8–3.8)	<0.001
pT2 vs. pT1	2.42	0.002	2.50	12.1 (1.6–93.4)	0.017
pT3 vs. pT1	3.49	<0.001	3.56	35.2 (4.8–258.6)	<0.001
pT4 vs. pT1	3.67	<0.001	3.79	44.4 (6.1–321.5)	<0.001
Lymphatic dissection D1 vs. lym-phatic dissection D2	-0.1	0.70	–	–	–
Combined operations vs. subtotal gastrectomy (distal and proximal)	0.53	0.01	–	–	–
Gastrectomy vs. subtotal gastrecto-my (distal and proximal)	0.30	0.067	–	–	–

The multivariate analysis results coincide with the literature data that the infiltrative forms of GC are associated with a high risk of developing metachronous PD [10]. The same is true for a metastatic lesion of the regional lymphatic collector, and the degree of such lesion correlates with the risk of developing carcinomatosis.

To develop a model of intraoperative PD risk assessment, we identified potential predictors by adapting the covariates mentioned in Table 2 for their possible intraoperative application. That is, during intraoperative prognosis, the covariate that described the pT category was simplified by combining T1, T2, T3 categories (pT4 category could be determined during intraoperative morphological examination). The simplification of the pT category made it possible to add a covariate that described the nature of the conducted surgical treatment to the final intraoperative prognosis model without the threat of retraining the model [11]. Besides, from the practical point of view, the "type of opera-

tion" covariate could be accurately determined intraoperatively. The pN category was also simplified by dividing it into cN0-1 and cN2-3 sub-categories. Such division was somewhat arbitrary since an accurate determination of the pN category was only possible after surgery, provided the removal of an adequate number of lymph nodes (Table 3).

Table 3 – Relative risk of developing metachronous PD (using the covariates adapted for intraoperative application)

Adverse outcome factors	Regression analysis results				
	Preliminary model		Final model		
	β	p	β	PR (95% CI)	p
Age	0	0.472	–	–	–
Gender male vs. female	-0.13	0.354	–	–	–
Diffuse-infiltrative vs. saucer-like + polypoid	0.82	< 0.001	0.84	2.3 (1.5–3.6)	< 0.001
Ulcer-infiltrative vs. saucer-like + pol-ypoid	1.31	< 0.001	1.32	3.7 (2.5–5.5)	< 0.001
N2-3 vs. N0-1	0.72	< 0.001	0.71	2.0 (1.5–2.7)	< 0.001
pT4 vs. pT1-3	0.94	< 0.001	0.93	2.5 (1.8–3.6)	< 0.001
Lymphatic dissection D1 vs. lymphatic dissection D2	-0.13	0.591	–	–	–
Combined operations vs. subtotal gas-trectomy	0.57	0.006	0.58	1.8 (1.2–2.7)	0.005
Gastrectomy vs. subtotal gastrectomy	0.44	0.008	0.46	1.6 (1.2–2.2)	0.004

Based on the multivariate analysis results (Table 3), we developed a PD development risk prediction model. The variables of this model were as follows:

$x1 = 1$ at combined gastrectomy or subtotal resection of the stomach, $x1 = 0$ at standard subtotal gastrectomy or gastrectomy;

$x2 = 1$ at standard gastrectomy, $x2 = 0$ at standard subtotal gastrectomy, with combined gastrectomy or subtotal gastrectomy;

$x3 = 1$ at diffuse infiltrative GC, $x3 = 0$ at ulcerative-infiltrative, polypoid or saucer-like pancreatic cancer;

$x4 = 1$ at ulcerative-infiltrative GC; $x4 = 0$ at diffuse-infiltrative, polypoid or saucer-like GC;

$x5 = 1$ at pN2-3, $x5 = 0$ at pN0 or pN1;

$x6 = 1$ at pT4a-b, $x6 = 0$ at pT1-3.

The hypothesis about the proportionality of risks (presence or absence of an agreement between the ranked Schoenfeld residuals) has been proven: p = 0.641. The model performance assessment (its suitability for prognosis) included calibration to prevent model re-training and bias and the assessment of the discriminatory power of the model. The performance was assessed by internal validation procedure [11] using bootstrapping with 1,000 repetitions by the performance indices presented in Table 4.

Table 4 – Model performance indicators

Indices	Model performance evaluation indices				
	Initial in-dex	Training set index	Test set in-dex	Δ between the test and training set in-dices	Refined in-dex
D_{xy}	0.584	0.588	0.577	0.011	0.572
D*	0.079	0.078	0.074	0.004	0.075
U**	-0.001	-0.001	0.0003	-0.001	0.0003
S***	1.0	1.0	0.969	0.031	0.969

Note: D – the discrimination index that characterizes the model's ability to distinguish between favorable and unfavorable prognosis groups; U** – the index of unreliability between the calibrated model and the initial data; S*** – the calibration bias to assess the agreement between the observed and predicted risks of developing an unfavorable outcome.*

The evaluation indices presented in Table 4 indicate an acceptable consistency (D_{xy} values), a satisfactory discriminatory ability (the discrimination index >0), the agreement (unreliability index approaches 0) of the developed model. A calibration bias close to 1 (0.969, in this case) indicated an acceptable general agreement between the observed and predicted risks of developing PD. The concordance index was 0.78.

The proposed formula for intraoperative determination of the risk of developing metachronous PD is based on the linear combination of predictors (Formula 1).

$$ПИ = 0,5793 \times x1 + 0,4555 \times x2 + \\ + 0,8354 \times x3 + 1,3158 \times x4 + \\ + 0,7122 \times x5 + 0,9275 \times x6 \quad (1)$$

Where *PI* is the prognostic index.

Formula 1 reflects the change in the relative risk logarithm depending on the values of the variables *x1-x6*. Formula 1 was used to calculate *PI* values and determine risk groups in the study cohort. The 33rd and 67th quantiles of the *PI* variable distribution were chosen as the boundary intervals of three risk groups: high-risk (*PI* > 1.75), intermediate-risk (0.85 > *PI* ≤ 1.75), or standard-risk (*PI* ≤ 0.85). The values presented in Table 5 can also be used to assess the probability of developing metachronous PD.

Table 5 – Likelihood of developing PD within 12, 24, or 36 months after radical surgery, by risk groups

Dissemination risk groups	Likelihood of developing PD, % / Duration of observation		
	12 months	24 months	36 months
Standard risk	1.2 ± 0.4	1.8 ± 0.6	2.2 ± 0.7
Intermediate risk	7.1 ± 1.4	10.7 ± 2.0	13.0 ± 2.5
High risk	23.2 ± 2.6	33.3 ± 3.5	39.2 ± 4.2

The choice of the observation period of 1 to 3 years to predict the probability of developing PD was justified by the maximum occurrence of progression cases within the first two years after surgery [1, 3]. The proposed method simplifies the prognosis of developing PD due to the use of a small number of prognostic factors that can be evaluated intraoperatively. Namely, high and standard risk can be established in the presence of 1) infiltrative cancer; 2) metastases in regional lymph nodes; 3) invasion of the serous membrane of the stomach. The disadvantage is a slight decrease in forecasting efficiency due to an unprecise determination of the pN category since a precise determination is based on the results of the postoperative histological examination.

Conclusion: The proposed formula-based prognostic model promotes intraoperative prediction of the expected likelihood of developing metachronous PD in patients radically operated for gastric cancer. The use of this information allows a differentiated approach to determining indications for preventive intraoperative ICT.

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