UDC 616.33-006-092-089-033.2: 617.55-006]-07
DOI http://doi.org/10.30978/GS-2022-1-28

ISSN 2786-5584 print
ISSN 2786-5592 online

A genomically stable molecular type of gastric cancer as a predictor of peritoneal relapse after radical surgical treatment

R. Yarema [1], M. Ohorchak [2], O. Petronchak [3], R. Huley [3], P. Hyrya [2], Y. Kovalchuk [2], V. Safiyan [2], O. Rilinh [2], M. Matusyak [2]

[1] Danylo Halytsky Lviv National Medical University
[2] Lviv Oncological Regional Treatment and Diagnostic Center
[3] West Ukrainian Histological Laboratory, Lviv

✉ Roman Yarema: roman.yarema@ukr.net

R. Yarema, PhD, MD (surgical oncologist), http://orcid.org/0000-0001-8314-7945
M. Ohorchak, MD (surgical oncologist)
O. Petronchak, MD (pathologist)
R. Huley, MD (pathologist)
P. Hyrya, MD (surgical oncologist)
Y. Kovalchuk, MD (surgical oncologist)
V. Safiyan, MD (surgical oncologist)
O. Rilinh, MD (surgical oncologist)
M. Matusyak, MD (surgical oncologist)

Peritoneal metastases are commonly associated with gastric cancer (GC) recurrence after radical treatment. Thus, patients at a high risk of peritoneal relapse require adjuvant intraperitoneal chemotherapy during the initial treatment. Along with clinical and morphological predictors of peritoneal relapse, another approach in surgical oncology is proving to be promising today. It refers to the prediction of the risk of developing metachronous peritoneal metastases in various molecular types of GC.

Objective — to study the risk of peritoneal relapse in patients with the genomically stable type of GC in comparison to its other molecular types.

Materials and methods. 37 patients with GC were enrolled into the study and evaluated after the radical treatment. 19 (51.4%) patients formed a subgroup with peritoneal relapse and 18 patients (48.6%) were included into a subgroup without metachronous carcinomatosis in the long term. All patients underwent immunohistochemical study for the E-cadherin (CDH1 gene) expression in a gastric tumor. The genomically stable molecular type was identified on the basis of the aberrant E-cadherin (CDH1-mutated) tumor phenotype detection.

Results. There was a statistically significant difference ($p=0.022$, $\chi^2=5.22$) in the degree of aberrant E-cadherin expression in subgroups of patients with and without peritoneal relapse — 68.4 and 33.3%, respectively. Hence, it was noted that the genomically stable molecular type had a significant influence on the risk of peritoneal recurrence: the 2-year peritoneal relapse-free survival of GC patients with E-cadherin of aberrant type was 31.6%, and in GC patients with wild-type E-cadherin expression — 71.4% ($p=0.022$). The 2-year overall survival of GC patients with aberrant type E-cadherin expression was 36.8%, whereas in GC patients with E-cadherin of the wild type — 77.8% ($p=0.003$).

Conclusions. The study found that the genomically stable molecular type of GC may serve as a predictive factor associated with an increased probability of peritoneal relapse, as well as a prognostic factor due to its negative impact on patient prognosis. The genomically stable molecular type of GC may be used as a tool for forming a cohort of patients with indications for adjuvant intraperitoneal therapy.

Keywords
gastric cancer, peritoneal relapse, genomically stable molecular type, E-cadherin, peritoneal metastases, intraperitoneal chemotherapy.

ARTICLE • Received 2022-28-02 • Received in revised form 2022-09-03

Currently, gastric cancer (GC) is the fifth most common cancer worldwide, with nearly one million new cases (5.6 % of all cancers) diagnosed in 2020 [12]. Peritoneal relapse is the most common pattern of GC recurrence [10, 15], which develops in 44.8 % of the 69.0 % of patients with serosal invasion after radical surgery [3, 10]. In order to reduce the risk of metachronous peritoneal carcinomatosis development, patients are advised to consider utilizing methods of adjuvant intraperitoneal chemotherapy at the initial stage of their treatment [6, 8, 11].

Thus, defining patients with a high risk of peritoneal recurrence and administering intraperitoneal chemotherapy to them still appears to be a challenge. Some pathological factors are associated with metachronous peritoneal metastasis: serosal invasion, diffuse infiltrative growth pattern, signet ring cell pathology, lymph node invasion, etc. [10]. Yet, in the age of precision medicine, patients get customized therapy designed based on molecular predictive factors [4]. The results of the next-generation sequencing available today enabled the creation of a molecular classification of GC. It distinguishes 4 molecular types of tumors: Epstein-Barr *virus* positive, microsatellite instability, genomically stable, and chromosomal instability [2].

The genomically stable type of GC is ultimately predetermined by the hereditary or somatic mutation of the CDH1 gene, coded by the cell-cell adhesion protein known as E-cadherin, and is characterized by the loss of E-cadherin expression on the cell membrane, which initiates the mobility of malignant cells. From the clinical perspective, the genomically stable type of GC is associated with the diffuse type of GC, according to the Lauren classification, and possesses a fairly strong affinity for peritoneal metastases [4].

Thus, the genomically stable type of GC, as a molecular predictor of peritoneal relapse, appears to be quite prospective. The identification of this molecular type may become an accurate tool in a complex personalized GC therapy. It may also allow us to identify patients who require adjuvant intraperitoneal therapy.

Materials and methods

Patients and specimens

The study is based on the analysis of the radical treatment effectiveness in 37 patients with localized and locally-advanced GC (pTis-4b, pN0-3b, M0) stages 0—IIIC. Of these patients, 19 (51.4 %) formed a subgroup with peritoneal relapse in the long term, and the remaining 18 (48.6 %) fell into a subgroup without metachronous carcinomatosis. These subgroups were selected as comparable pools of patients by qualitative composition regarding sex, age, the number of patients with the serous membrane invasion of the stomach, and the number of patients with the diffuse GC type (Table 1). The patients received treatment at the Department of Abdominal Surgery of the Lviv State Oncology Regional Treatment and Diagnostic Center in 2013—2018 (prospective clinical study). The ages of patients ranged from 42 to 76 years, and the average age was 60.23 ± 8.28 years. The diagnosis of GC in all patients was verified morphologically prior to the treatment onset. The GC study was conducted based on criteria from the TNM 7th edition classification (2009).

An immunohistochemical study of E-cadherin expression (CDH1 gene) was performed in 37 patients. The genomically stable molecular type was determined after the aberrant E-cadherin (CDH1-mutated) tumor phenotype had been confirmed.

Immunohistochemistry assay

The tissue specimens were deparaffinized with xylene, rehydrated for antigen retrieval. Phosphate buffered saline was used to wash the slides, followed by treatment with 3 % hydrogen peroxide for 20 min to quench endogenous peroxidase activity. Then, the samples were preincubated with 10 % goat serum at room temperature for 30 min to prevent nonspecific staining. The sections were incubated with the following primary antibodies: Mouse anti-human Cadherin E Monoclonal Antibody (Clone HECD-1, MAD-000761Q — 1 : 50 dilution) 20 min in a humidified container, washed with phosphate buffered saline and the tissue slides were treated with a «UltraVision Quanto detection system HRP» by Thermo Scientific and stained with 3,3-diaminobenzidine tetrahydrochloride. Lastly, the sections were counterstained with Mayer's hematoxylin, dehydrated

Table 1. **Primary clinical and pathological characteristics of patients depending on the presense of relapse in the long term**

Characteristics	With peritoneal relapse (n = 19)	Without peritoneal relapse (n = 18)
Men	8 (42.1 %)	8 (44.4 %)
Women	11 (57.9 %)	10 (55.5 %)
Age, years	58.0 ± 6.18	61.0 ± 9.12
Without serosal invasion	2 (10.5 %)	2 (11.1 %)
With serosal invasion	17 (89.5 %)	16 (88.9 %)
Diffuse type of GC	16 (84.0 %)	15 (83.0 %)
Intestinal type GC	3 (16.0 %)	3 (17.0 %)

and mounted. We replaced the primary antibody with normal goat serum to obtain a negative control. The semi-quantitative immunohistochemistry results were evaluated by two independent pathologists who were blinded to the patients' clinical and biochemical information and the stained tissue sections were evaluated using a scale as follows: wild type — with preservation of membrane or cytoplasmic E-cadherin expression and aberrant type — with complete loss or expression < 10 % of cells.

Follow-up

Patients were regularly followed-up after the operation. We performed ultrasonography every 3 months and chest radiography every 6 months during the first two postoperative years and every 6 months thereafter. Patients with inconclusive ultrasonography results underwent computerized tomography. Peritoneal relapse-free survival (PRFS) was measured from the date of surgery to the date of peritoneal recurrence or the final follow-up exam. Overall survival (OS) was measured from the date of surgery to the date of death or the last follow-up exam. The study was approved by the University Ethical Committee, which complied with the Declaration of Helsinki of 1975. Written informed consent was provided by all patients examined.

Statistical analysis

Statistical analysis of the primary data was performed using SPSS 22 and Statistica 6 software. The censored Kaplan-Meier method was used to study the cumulative survival of patients, whereas the reliability of the survival difference in certain groups was determined using a log-rank coefficient. A multivariate analysis was performed using the χ^2 index and the Cox model. To test statistical correlations, Pearson's linear correlation coefficient was used.

Results and discussion

Wild (with preservation of membrane or cytoplasmic expression) and aberrant (with complete loss or expression < 10 % of cells) types of E-cadherin were observed in both diffuse (Fig. 1) and intestinal (Fig. 2) types of GC.

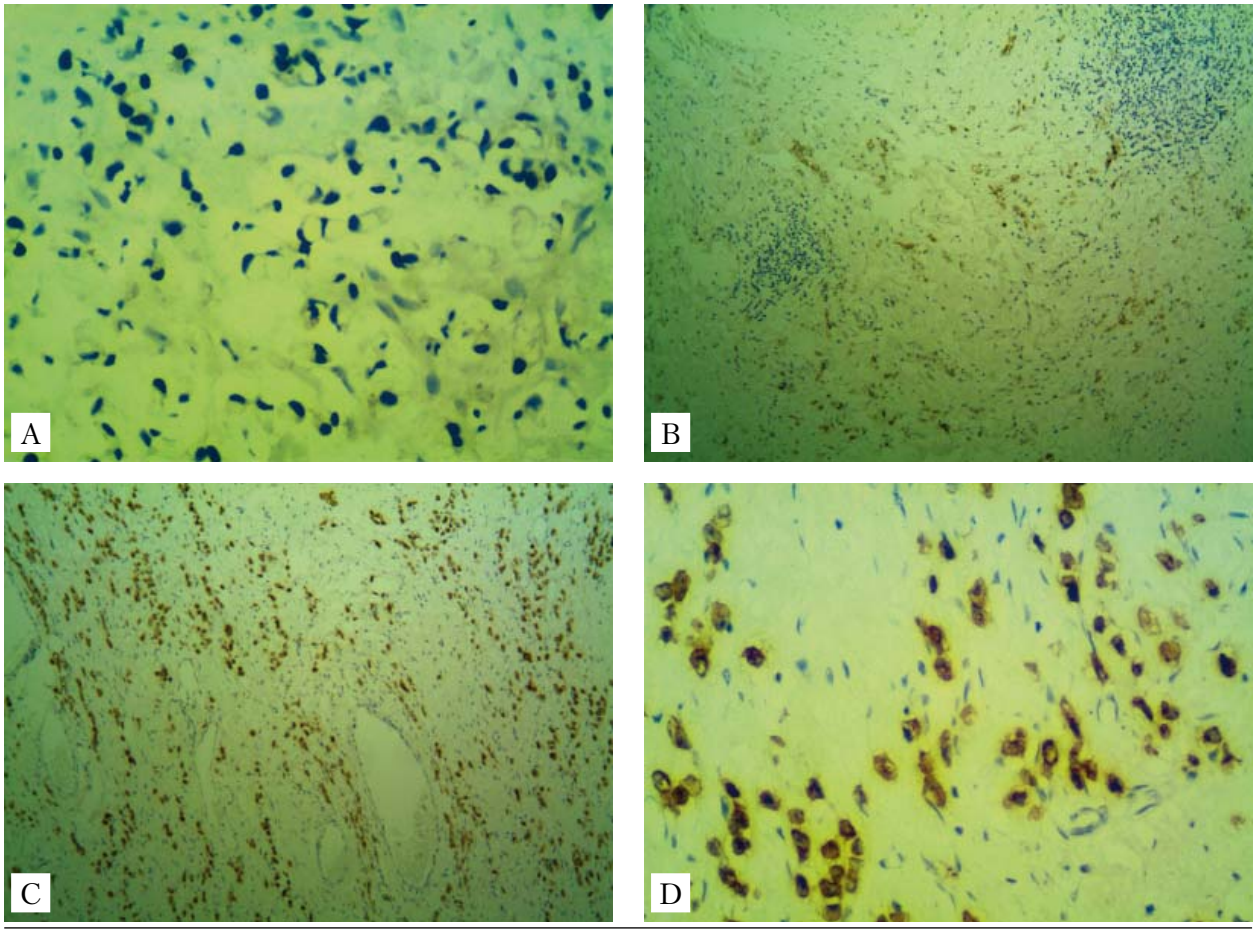

Figure 1. **Expression of E-cadherin in the histological specimen of diffuse gastric cancer: A — classic variant of the expression loss in signet-ring cell GC, aberrant type, × 400; B — preservation of membrane expression, wild type, × 100; C — preservation of membrane and cytoplasmic expression, wild type, × 100; D — preservation of membrane and cytoplasmic expression, wild type, × 200**

In subgroups of patients with and without intraperitoneal recurrence, there was a statistically significant difference ($p = 0,022$, $\chi^2 = 5,22$) in the presence of an aberrant type of E-cadherin expression (corresponding to the genomically stable molecular type of GC) — 68.4 % and 33.3 %, respectively.

In the diffuse GC type, the genomically stable type was found twice as often in patients with peritoneal relapse as in patients without peritoneal recurrence. All three cases of intestinal peritoneal recurrence of GC were characterized by loss of E-cadherin expression (Table 2).

Aberrant E-cadherin type statistically significantly worsened the relapse-free and overall survival of patients (Table 3, Fig. 3).

A statistically significant effect of aberrant E-cadherin in GC (genomically stable molecular type) on the risk of intraperitoneal recurrence was found due to the fact that the 2-year peritoneal relapse-free survival of patients with E-cadherin of the aberrant type in GC was 31.6 % against 71.4 % for patients with E-cadherin of the wild type in GC ($p = 0.022$) (Fig. 4).

Peritoneal relapse is the most common pattern of recurrence after the radical treatment of GC [15]. Peritoneal recurrence may relate to the intraoperative peritoneal dissemination that results from surgical manipulations [13]. However, the first and foremost reason for that is the presence of a microscopic pool of tumor cells in the peritoneum before the time of surgery, which derives from the biologic features of a tumor [4]. Previous research showed a strong affinity for metachronous peritoneal metastases in the diffuse type, undifferentiated and signet ring cell pathology [10, 15]. In order to reduce the level of peritoneal relapse in such patients, the whole range of adjuvant intraperitoneal chemotherapy methods is offered today, namely: hyperthermic intraperitoneal

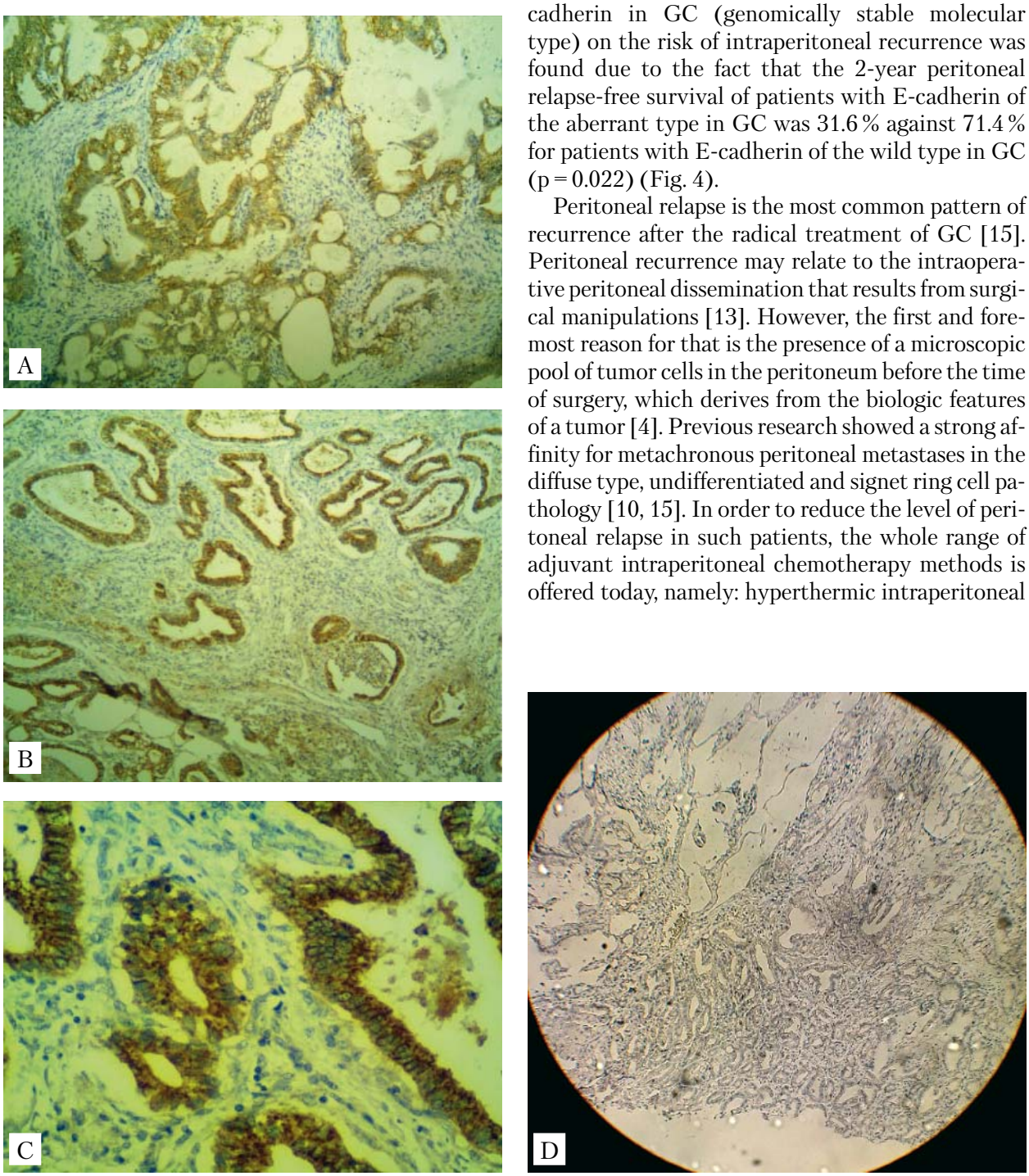

Figure 2. **Expression of E-cadherin in a histological specimen of an intestinal type of gastric cancer: A — classic variant of preservation of membrane expression, wild type, × 100; B — classical variant of preservation of membrane and cytoplasmic expression, wild type, × 100; C — classic variant of preservation of membrane and cytoplasmic expression, wild type, × 200; D — loss of expression, aberrant type, × 100**

Table 2. **The frequency of the genomically stable molecular type in GC patients based on the histological type by Lauren classification and peritoneal relapse**

Characteristics	With peritoneal relapse in the long term (n = 19)	Without peritoneal relapse in the long term (n = 18)
Aberrant E-cadherin type	13 (68.4 %)	6 (33.3 %)
Wild E-cadherin type	6 (31.6 %)	12 (66.7 %)
Diffuse type of GC		
Aberrant E-cadherin type	10 (62.5 %)	5 (33.3 %)
Wild E-cadherin type	6 (37.5 %)	10 (66.7 %)
Intestinal type of GC		
Aberrant E-cadherin type	3 (100.0 %)	1 (33.3 %)
Wild E-cadherin type	0	2 (66.7 %)

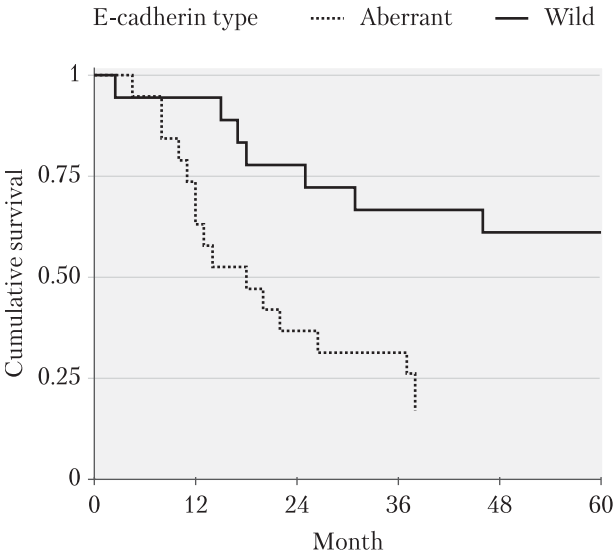

Figure 3. **Overall survival of patients with gastric cancer based on E-cadherin status**

Table 3. **The survival of GC patients based on E-cadherin status**

Indicator	Aberrant type	Wild type	p
2-year disease-free survival, %	31.6	66.7	0.004
Median disease-free survival, months	13	Not achieved	0.005
2-year overall survival, %	36.8	77.8	0.003
Median overall survival, months	18	Not achieved	0.004

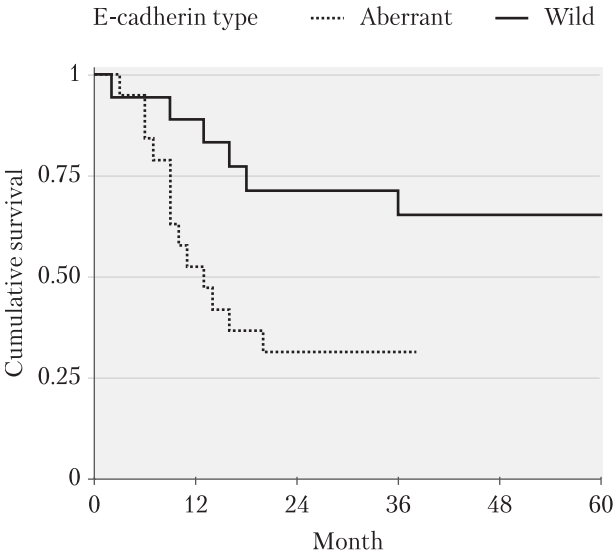

Figure 4. **Peritoneal relapse-free survival in gastric cancer patients based on E-cadherin status**

chemotherapy (HIPEC), early postoperative intraperitoneal chemotherapy (EPIC), extensive intraoperative peritoneal lavage (EIPL), etc. [6, 8, 9, 11]. Thus, in clinical practice, the study of prospective predictive factors for peritoneal relapse in GC cases, including molecular factors, may serve as a powerful tool for forming a cohort of patients with indications for adjuvant intraperitoneal therapy [14].

Germinogenic (hereditary) or somatic mutations in the gene CDH1, as well as its posttranslational disorders during carcinogenesis, cause the loss of E-cadherin expression on the surface of gastric carcinoma cells, resulting in their mobility and desquamation from the surface of the primary tumor on the serous membrane of the stomach. The presence of free malignant cells in the abdominal cavity, which have the potential for mesothelial adhesion or direct absorption into the sub-mesothelial layers through the lymphatic «hatches» of the peritoneum, is an integral part of the initiation of early stages of peritoneal metastasis of GC. The development of further stages of intraperitoneal carcinogenesis depends on the «favorable» factors for the tumor, which are regulated by autocrine and paracrine pathways [4].

In our research, the aberrant type of E-cadherin expression (that corresponds to the genomically stable molecular type of GC) was detected twice as often (68.4 %) in the subgroup of patients with peritoneal recurrence as in the subgroup without evidence of the latter (33.3 %, p = 0.022, $\chi^2 = 5.22$). Respectively, this molecular type of GC is

distinguished as a basic factor triggering the peritoneal dissemination processes of GC. For instance, in the diffuse GC type, two thirds of patients (62.5 %) with intraperitoneal recurrence were defined as aberrant E-cadherin type, while in the diffuse GC subgroup without intraperitoneal recurrence, the aberrant E-cadherin type was observed only in 33.3 % of patients. In addition, there were two cases of peritoneal relapse of the diffuse GC type without serous invasion, in which the loss of E-cadherin expression was determined — this confirms the aggressiveness and high potential for peritoneal metastasis of the genomically stable GC type. On the other hand, the intestinal type of GC is rarely accompanied by the development of metachronous peritoneal metastases [15]. Also, three cases of peritoneal relapse were observed in our study. They occurred along with the intestinal GC type; the loss of E-cadherin expression was detected in all these patients. These results prove the initiating and distinctive pathogenetic role of poor E-cadherin expression in the intraperitoneal recurrence processes for both (diffuse and intestinal) types of GC. Clinically, these results suggest that for the diagnosis of the genomically stable GC it is not sufficient to have histological evidence of diffuse type (which undoubtedly comprises the largest segment of the genomically stable type), whereas the evaluation of E-cadherin expression is necessary. The results of the monofactor analysis of our study have proved the statistically prospective influence of the aberrant type of E-cadherin expression on the risk of peritoneal recurrence, as well as the prospective deterioration of the recurrence-free and overall survival of patients. Other authors have also reported an increased risk of peritoneal relapse and a decreased prognosis in patients with aberrant E-cadherin [5, 7].

Thus, the loss of E-cadherin expression and the formation of the genome-stable molecular type GC phenotype is a key pathogenetic mechanism for triggering peritoneal GC metastasis, which is able to realize its potential even in intestinal GC or no serous gastric invasion. From a clinical standpoint, there is every reason to consider this molecular type as a predictive factor for the development of peritoneal relapse after radical surgical treatment of GC, as well as a prognostic factor due to its negative impact on patient prognosis.

Conclusions

The study found that the genomically stable molecular type of GC may serve as a predictive factor associated with an increased probability of peritoneal relapse, as well as a prognostic factor due to its negative impact on patient prognosis. The genomically stable molecular type of GC may be used as a tool for forming a cohort of patients with indications for adjuvant intraperitoneal therapy.

Declaration of interests

The authors declare that they have no conflicts of interest.

The authors declare no proprietary, financial, or other personal interests related to this article.

Ethics approval and written informed consents statements

The study was approved by the University Ethical Committee, which complied with the Declaration of Helsinki of 1975. Patients gave written informed consent prior to study inclusion.

Author contributions

Conception and design — R. Yarema, M. Ohorchak; acquisition of data — R. Yarema, M. Ohorchak, O. Petronchak, P. Hyrya, Y. Kovalchuk, V. Safiyan, O. Rilinh, M. Matusyak; analysis and interpretation of data — R. Yarema, M. Ohorchak, O. Petronchak, R. Huley, P. Hyrya, Y. Kovalchuk, V. Safiyan, O. Rilinh, M. Matusyak; drafting the article, critical revision of the article — R. Yarema.

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Геномностабільний молекулярний тип раку шлунка як предиктор інтраперитонеального рецидиву після радикального хірургічного лікування

Р. Ярема[1], М. Огорчак[2], О. Петрончак[3], Р. Гулей[3], П. Гиря[2], Ю. Ковальчук[2], В. Сафіян[2], О. Рилінг[2], М. Матусяк[2]

[1] Львівський національний медичний університет імені Данила Галицького

[2] Львівський онкологічний регіональний лікувально-діагностичний центр

[3] Західноукраїнська гістологічна лабораторія, Львів

Найчастішим шляхом рецидивування раку шлунка (РШ) після радикального хірургічного лікування є імплантаційні метастази. Такі хворі з високим ризиком інтраперитонеального рецидиву потребують ад'ювантної внутрішньочеревної терапії під час первинного лікування. Окрім клініко-морфологічних предикторів інтраперитонеального рецидиву, перспективним напрямом у хірургічній онкології є вивчення ризику метахронних перитонеальних метастазів при різних молекулярних типах РШ.

Мета — вивчити ризик інтраперитонеального рецидиву при геномностабільному типі РШ на тлі інших молекулярних типів.

Матеріали та методи. Проведено аналіз результатів радикального хірургічного лікування 37 хворих на РШ, із них 19 (51,4 %) з інтраперитонеальним рецидивом та 18 (48,6 %) без метахронного карциноматозу у віддалений період. У всіх хворих проведено імуногістохімічне дослідження експресії Е-кадгерину (ген CDH1) у пухлині шлунка. Геномностабільний молекулярний тип реєстрували у разі визначення Е-кадгерин аберантного (CDH1-мутованого) фенотипу пухлини.

Результати. Виявлено статистично значущу різницю ($p = 0,022$, $\chi^2 = 5,22$) за наявністю аберантного типу експресії Е-кадгерину між хворими з інтраперитонеальним рецидивом та без такого — 68,4 і 33,3 % відповідно. Установлено вірогідний вплив геномностабільного молекулярного типу на ризик метахронного карциноматозу: дворічна виживаність без інтраперитонеального рецидиву хворих на Е-кадгерин аберантний тип РШ становила 31,6 %, хворих на Е-кадгерин дикий тип РШ — 71,4 % ($p = 0,022$), дворічна загальна виживаність — відповідно 36,8 та 77,8 % ($p = 0,003$).

Висновки. Визначено вірогідну предиктивну щодо інтраперитонеального рецидиву та негативну прогностичну роль геномностабільного молекулярного типу РШ. Наявність останнього можна використовувати як інструмент для виділення групи хворих, яким необхідні ад'ювантні методи інтраперитонеального впливу.

Ключові слова: рак шлунка, інтраперитонеальний рецидив, геномно-стабільний молекулярний тип, Е-кадгерин, перитонеальні метастази, інтраперитонеальна хіміотерапія.

FOR CITATION

Yarema R, Ohorchak M, Petronchak O, Huley R, Hyrya P, Kovalchuk Y, Safiyan V, Rilinh O, Matusyak M. A genomically stable molecular type of gastric cancer as a predictor of peritoneal relapse after radical surgical treatment. General Surgery (Ukraine). 2022:1;28-34. http://doi.org/10.30978/GS-2022-1-28.