

THE RESULTS OF THE JAPANESE GASTRIC CANCER ASSOCIATION MORPHOLOGICAL CLASSIFICATION ADAPTATION FOR THE KAZAKH POPULATION

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ABSTRACT

Relevance: Gastric cancer (GC) morbidity is growing in Kazakhstan every year. In 2022, 2 915 new GC cases were detected (15 per 100,000 population), making GC the third most common cancer. The early detection rate of GC does not exceed 10-20%, and advanced forms of GC are over 40%. Mortality increases in the first year after the diagnosis (up to 40%).

The best way of solving early detection of gastric cancer is carrying out diagnostics at the stage of pre-tumor stomach diseases. Timely diagnosis and treatment of surgical and borderline diseases of the upper gastrointestinal tract (metaplastic and dysplastic changes in the mucous membrane of the esophagus, stomach, and duodenum and adenocarcinomas and early cancer arising against this background) are a complex medical and social problem.

Endoscopic methods for diagnosing esophagus, stomach, and duodenum diseases are the most highly informative nowadays. However, precancerous changes (atrophy, metaplasia, and dysplasia) in conventional endoscopic examination may not have specific features. It is necessary to improve the results of endoscopic diagnosis. The chromoscopy method may be one of the methods used to identify precancerous pathology and GC methods.

The study aimed to increase the efficiency of early detection of gastric cancer by adapting the Japanese Gastric Cancer Association (JGCA) morphological classification for the Kazakh population.

Methods: We conducted endoscopic studies of 500 residents of the Republic of Kazakhstan using chromoscopy and morphological studies of the biopsy obtained during endoscopic examination. These patients had digestive system problems but previously did not have a GC diagnosis. We formed the risk groups according to JGCA (editions 13th and 14th).

Results: We identified 3(0.6%) morbidity of severe dysplasia according to the results of 500 patients' biopsy samples morphological study. This morphological structure is classified as a well-differentiated adenocarcinoma. We recommended a surgical treatment for identified patients.

Conclusion: The detected cases of obligate pre-cancer with an extremely high probability of malignancy prove the importance of using the JGCA classification for GC early diagnostics and allow us to recommend the use of chromoscopy in endoscopic examination of the stomach.

Keywords: gastric cancer (GC), chromoscopy, severe dysplasia, morphological classification of the Japanese Gastric Cancer Association (JGCA).

Introduction: According to the national cancer registry, the number of newly diagnosed gastric cancer (GC) cases is growing annually in Kazakhstan, increasing by 1.9% in 2021 and 11.0% in 2022. However, it declined by 2.5% in 2018 and 8.1% in 2020. In 2022, 2,915 new cases of GC were revealed (15 per 100,000 population). GC ranked 3rd in the structure of oncopathology (8.3%) in both sexes, 2nd in men (12.5%), and 6th in women (5.12%) [1]. In 2020, GC ranked 2nd in the structure of deaths from cancer in Kazakhstan, with a one-year lethality of 44.1% in 2021 and 40.0% in 2022. The ratio between one-year mortality and advanced cases (stage IV) was 2.2 in 2021 and 1.9 in 2022

[1]. It is worth noting that the annual mortality rate reaches 40.0%, while the early detection rate for GC does not exceed 10-20%. Over 40% of cases are detected at stages III-IV of the disease [2].

Early diagnostics followed by the treatment of precancerous diseases of the gastrointestinal mucosa (atrophic, metaplastic, and dysplastic changes of the mucous membrane of the esophagus, stomach, and duodenum) is a daunting challenge for the oncology service [3-5].

These facts urge the search for methods of new early diagnostics at the stage of precancerous lesions and improved treatment efficacy for stomach diseases. A com-

plicated, controversial issue in early GC diagnostics is the discrepancy in assessing the condition of patients with newly established GC or precancerous diseases. First, it stems from different malignant neoplasm (MN) classifications adopted in various countries, which ultimately affect the adequacy of a patient's condition assessment to assign this patient to a particular risk group.

For example, the Japanese MN classifications adopted in 1998-2010 were not used in European and American clinics due to their more complex numbering of regional lymph nodes and significant differences from the UICC international classification [6-9].

The second, equally important point in the Japanese Classification of Gastric Carcinoma indicates the tumor's predominant location in the stomach (C – upper part, M – middle part, A – lower part). The degree of tumor invasion into the stomach wall is denoted by the index S, pointing out the invasion of serosa: S₀ – no invasion of serosa; S₁ – suspect for invasion of serosa; S₂ – the invasion of serosa; S₃ – tumor invasion into the neighboring organs [7, 8].

The third distinction between the Japanese and the generally accepted European classifications is the more detailed description of the lymph node condition. The Japanese classification considers the number and the group of lymph nodes (groups I-IV); each group is numbered depending on the lymph node size (1 to 16 cm). Usually, Japanese oncologists perform histological examination of up to 30 lymph nodes. In contrast to the commonly accepted European classification, the Japanese one uses "P" and "H" instead of the "M" symbol, where "H" characterizes the presence of metastases in the liver and their number (H₀ – no metastases in the liver, H₁ – the presence of metastases in one lobe of the liver, H₂ – the presence of several metastases in both lobes of the liver, H₃ – the presence of multiple metastases in the liver), and "P" is the degree of tumor dissemination over the peritoneum (P₀ – no peritoneal metastases, P₁ – the presence of dissemination in the peritoneum above the colon, P₂ – the presence of separate sites of dissemination on the peritoneum distant from the stomach; P₃ – the presence of multiple dissemination in the abdominal space). Considering all differences in the compared classifications, the GC stages are designated as follows: S₀N₀P₀H₀ – stage I, S₁N₀₋₁P₀H₀ – stage II, S₂N₀₋₂P₀H₀ – stage III, S₃N₃₋₄P₁₋₃H₁₋₃ – stage IV [7, 8].

Since the release of the 14th edition of the classification (2010) recommended by the Japanese Gastric Cancer Association (JGCA), the previous classification was remodified and brought closer to the commonly accepted international one. In the new classification, the lymph node dissection is taken into account only depending on the type of surgery (resection, gastrectomy), and the category N is taken into account by the number of nodes affected by the tumor [4-11].

Endoscopic methods of diagnosing gastrointestinal tract diseases are the most informative from the point of view of the amount of information [4]. However, conventional endoscopic examination, even when the high-tech equipment of the latest generation is used, makes it challenging to diagnose the degree of atrophic, metaplastic,

and dysplastic changes in the mucous membrane that may be the cause of malignant neoplasm development [5]. This is especially essential in screening for MNs of the gastrointestinal tract [12-18].

Chromoscopy is a method to detect precancerous pathologies and GC. Even though chromoendoscopy has shown the potential to expand the use of endoscopic studies in diagnosing gastric diseases in some countries, Kazakhstan started to apply this method only in 2021. Therefore, there is a need to adapt the JGCA morphological classification for the population of Kazakhstan. This method focuses on the early detection of GC to perform organ-preserving surgery to rapidly recover these patients' working ability and improve their quality of life. Therefore, we applied several internationally recognized classifications to assess the findings of conducted morphological examinations.

The project aims to improve endoscopic diagnostics of GC using chromoscopy.

The study aimed to increase the efficiency of early detection of gastric cancer by adapting the Japanese Gastric Cancer Association (JGCA) morphological classification for the Kazakh population.

Materials and Methods: The JGCA morphological classification was adapted for the Kazakh population during the morphological study of biopsy material obtained from 500 endoscopic examinations (using chromoscopy by methylene blue staining) of Kazakhstani residents aged 40 and above. The inclusion criterion was the presence of "gastric problems" but without a previously diagnosed "gastric cancer." The study was carried out in four oncology centers: "The Kazakh Institute of Oncology and Radiology" JSC, Almaty (170 examinations), "Multidisciplinary Center of Oncology and Surgery" MSE on REM of the Healthcare Department of East Kazakhstan in Ust-Kamenogorsk (142 examinations), "Center for Nuclear Medicine and Oncology" MSE on REM of the Healthcare Department of Abay region in Semey (69 examinations), and "Atyrau Regional Oncology Dispensary" MSE on REM in Atyrau (119 examinations). The JGCA classification was used to interpret the findings of the morphological examination of biopsy material obtained during chromoscopy in addition to the generally accepted European classification since the Japanese classification considers factors that significantly impact the prognosis. According to the JGCA classification, patients with severe dysplasia were classified as at high risk of developing GC. After clarification of the diagnosis, they were classified as patients with high-grade GC adenocarcinoma.

Results: The analysis of the results of 500 patients examined in four regions of Kazakhstan showed that their average age was 67.74±2.61 years, suggesting that the patients were mainly older. The χ^2 test showed a statistically significant correspondence between the sex and the GC detection: $\chi^2=45.97$; $df=1$; $p=0.000$. The GC was statistically less common in women than the expected MN=-4.2; $p<0,001$. Statistically, the odds for detection of GC in men were significantly higher than in women: OR=2.471, CI=1.883-3.242.

The findings of the endoscopic examination (by chromoscopy) of 500 patients from four regions of Kazakhstan showed the following results according to the generally accepted European classification: stomach without pathology – 0 cases, inflammatory diseases of the stomach – 439, stomach ulcer – 14 (3 patients had severe dysplasia), gastric submucosal tumor – 7, gastric polyp with a thin pedicle – 2, a gastric polyp on a wide pedicle – 5, malignant gastric tumor up to 3 cm in size – 13, and malignant gastric tumor over 3 cm – 20 patients. However, three of 14 patients in the “GS 4 stomach ulcer” group had severe dysplasia (obligate pre-cancer), so they were assigned to a separate risk group under the JGCA morphological classification (Table 1). Those patients were recommended surgical treatment.

The χ^2 criterion showed a statistically significant correspondence between the locations of the surveyed by region and the study findings: $\chi^2=57.47$; $df=10$; $p=0,000$. For example, for the “city” location, when compared to expected, less frequently have been statistically detected, the re-

sults of “GS7. Gastric polyp with a wide pedicle” ($MN=-2.2$; $p<0.05$) and “GS11. Malignant gastric tumor with a focus over 3 cm, pathomorphologically verified” ($MN=-3.1$; $p<0.01$). For the “village” location, when compared to expected, more frequently have been statistically detected the results of “GS7. Gastric polyp with a wide pedicle” ($MN=2.7$; $p<0.05$) and “GS11. Malignant gastric tumor with a focus over 3 cm, pathomorphologically verified” ($MN=3.8$; $p<0.01$).

In light of the study findings, we adapted the JGCA morphological classification and developed an algorithm for GC detection at the earliest stage of the disease (Figure 1). According to this algorithm, the findings of a pathomorphological examination of biopsy material obtained during chromoendoscopy (after morphological verification of the pathological site) shall be reviewed to assign the patient to one of the three risk groups: pre-cancer, severe dysplasia (according to the morphological classification with consideration of the JCGA adaptation), or cancer. Further patient routing depends on their risk group.

Table 1 – Distribution of cases under the adapted morphological classification of the Japanese Gastric Cancer Association (using chromoscopy (n=500))

Distribution into groups based on study results	Total cases, abs. (%)	
	Under the European morphological classification	Under the European morphological classification with the account of the adapted JGCA classification
GS 1 Stomach without pathology	-	-
GS 2 Hereditary stomach diseases, con-genital abnormalities	-	-
GS 3 Inflammatory diseases of the stom-ach	439 (87.8%)	439 (87.8%)
GS 4 Stomach ulcer	14 (2.8%)	11 (2.2%)
GS 5 Gastric submucosal tumor	7 (1.4%)	7 (1.4%)
GS 6 Gastric polyp with a thin pedicle	2 (0.4%)	2 (0.4%)
GS 7 Gastric polyp with a wide pedicle	5 (1.0%)	5 (1.0%)
GS 8 Malignant gastric tumor with a fo-cus up to 3 cm, without morphological verification (double gastroscopy)	-	-
GS 9 Malignant gastric tumor with a fo-cus of up to 3 cm, pathomorphologically verified	13 (2.6%)	13 (2.6%)
GS 10 Malignant gastric tumor with a focus size of larger than 3 cm, without morphological verification (double gas-troscopy)	-	-
GS 11 Malignant gastric tumor with a focus size of larger than 3 cm, pathomor-phological verified	20 (4.0%)	20 (4.0%)
Severe dysplasia (obligate pre-cancer)*	-	3 (0.6%)
Total number	500	500

Note: *Severe dysplasia (obligate pre-cancer) under the morphological classification of the Japanese Gastric Cancer Association

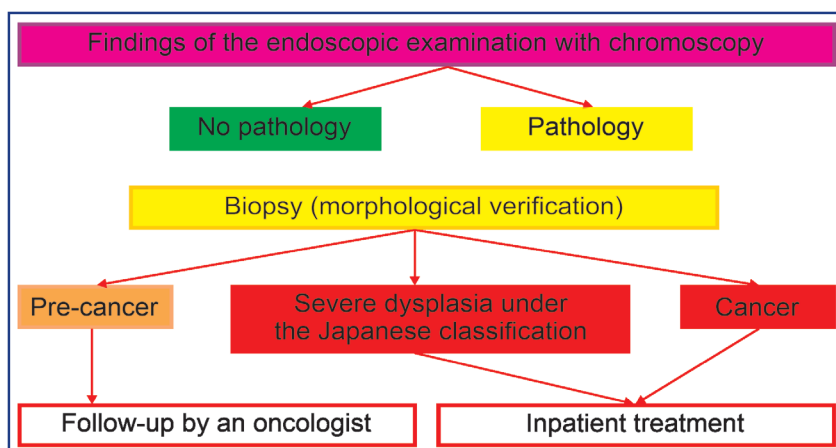


Figure 1 – Algorithm of endoscopic examination with chromoscopy with the account of the adapted morphological classification of the Japanese Gastric Cancer Association

Discussion: The proposed algorithm of endoscopic examination of the stomach with chromoscopy with the account of the adapted JGCA classification provides an attending physician with the results that help to choose an appropriate treatment method at an earlier stage of the disease. However, different approaches to GC classification in Japan and Western countries make it very difficult to compare the treatment outcomes of the two surgery schools.

A distinctive feature of GC diagnostics from the JGCA standpoint is a different approach to determining the morphological form: severe dysplasia is classified as a well-differentiated adenocarcinoma, and these patients undergo surgical treatment [11, 12]. This aspect has been tested in this study.

The Japanese classification considers the factors that significantly impact the disease prognosis. First, the chromoscopy method is based on the exceptional properties of methylene blue used for vital staining of the mucous membrane of the digestive tract epithelium. This allows visual detection of lesions during endoscopy and taking a biopsy from the most suspicious site. At that, the dye pigment binds to glycogen contained in the tissues. The afflicted mucous membrane is not stained, even at the earliest stage of the disease, because glycogen is found only in healthy cells. Unstained spots on the mucosa are well visible during endoscopy and require further examination. Thus, the probability of detecting cancer at stages 0 and I approaches 100%.

The difference from the generally accepted European classification is that the Japanese standards, represented by the JCGA morphological classification, are evident and detailed due to using a more accurate endoscopic examination method by applying chromoscopy. For example, in our study, the JGCA classification allowed identifying patients who would not be assigned to any groups under the generally accepted European classification widely used by clinicians in most countries. Morphological examination of biopsy materials obtained during 500 chromoscopy procedures to form a risk group based on the JCGA morphological classification revealed 3 (0.6%) cases with severe dysplasia. These three cases were determined to be obligate precancerous lesions with an extremely high likelihood of malignancy. The JCGA morphological classification (editions 13 and 14) determines this morphological structure as a well-differentiated adenocarcinoma. Therefore, all three patients diagnosed with severe dysplasia were assigned to a high-risk group and recommended surgical treatment.

Conclusion: The detected three cases of obligate pre-cancer with an extremely high probability of malignancy prove the importance of using the JGCA classification for GC early diagnostics and allow us to recommend the use of chromoscopy in endoscopic examination of the stomach. This approach is justified since severe dysplasia of the gastric mucosal epithelium can indicate the presence of undetected adenocarcinoma foci, which is essential for GC early detection at stages 0-I.

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АНДАТПА

ЖАПОН АСҚАЗАН ОНЫРЫ ҚОҒАМЫНЫҢ МОРФОЛОГИЯЛЫҚ ЖІКТЕМЕСІН ҚАЗАҚСТАН ХАЛЫҚЫНА БЕЙІМДЕУ НӘТИЖЕЛЕРІ

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Өзектілігі: Қазақстанда жыл сайын асқазан обыры (АО) ауруларының саны артып келеді. Сонымен, 2022 жылы 2915 адам анықталды (100 000 тұрғынға 15 адам), онкопатология құрылымында 3 орынды алады, бұл ретте асқазан обырының ерте формаларын анықтау көрсеткіші 10-20%-дан аспайды, асқынған түрлері – 40%-дан жоғары; Диагноз қойылған сәттен бастап бірінші жылы өлім-жітім артады (40% дейін).

Бастапқы кезеңде асқазанның обыры алды ауруларының сатысында диагностика жүргізу асқазан обырын ерте диагностикалау мәселесін шешудің жолы болып табылады. Жоғарғы асқазан-ішек жолдарының хирургиялық және шекаралық ауруларын (өңештің, асқазанның және он екі елі ішектің шырышты қабатындағы метапластикалық және диспластикалық өзгерістер мен аденокарциномалар және осы фоннан туындаған ерте обыры) дер кезінде диагностикалау және емдеу күрделі медициналық-әлеуметтік мәселе болып табылады.

Қазіргі уақытта өңештің, асқазанның және он екі елі ішектің ауруларын диагностикалаудың эндоскопиялық әдістері ең ақпараттылығы жоғары. Дегенмен, әдеттегі эндоскопиялық зерттеу кезінде обырға дейінгі өзгерістер (атрофия, метаплазия, дисплазия) ерекше белгілерге ие болмауы мүмкін. Осыған байланысты эндоскопиялық диагностика нәтижелерін жақсарту жолдарын іздестіру қажет. Қатерлі обырға дейінгі патология мен асқазан қатерлі обырын анықтауға бағытталған әдістердің бірі хромоскопия әдісі.

Зерттеудің мақсаты – Жапон асқазан обыры қоғамының (JGCA) морфологиялық жіктелімін Қазақстан халықна бейімдеу арқылы асқазан обырының ерте диагностикасының тиімділігін арттыру.

Әдістері: Хромоскопиялық әдіспен эндоскопиялық зерттеулер Қазақстан Республикасының 500 асқорыту жүйесі аурулары, ауруларын анықталған асқазан обыры диагнозы жоқ және эндоскопиялық зерттеу кезінде алынған биопсияның морфологиялық зерттеулері, тәуекел тобын құра отырып жүргізілді. Жапон асқазан обыры қоғамына (JGCA) сәйкес (13-ші және 14-ші жасрияланымдар).

Нәтижелері: 500 науқастан алынған биопсия үлгілерін морфологиялық зерттеу нәтижелері бойынша ауыр дисплазиясы бар 3(0,6%) жағдай анықталды. Бұл морфологиялық құрылым жақсы дифференциацияланған аденокарцинома ретінде жіктеледі. Анықталған науқастарға хирургиялық емдеу ұсынылады.

Қорытынды: Осылайша, қатерлі обырына айналу ықтималдығы өте жоғары міндетті қатерлі обырына дейінгі жағдайлары асқазан обырын ерте диагностикалау үшін Жапон асқазан обыры қоғамының (JGCA) морфологиялық жіктелімін қолданудың маңыздылығын дәлелдейді және асқазанды эндоскопиялық зерттеуде хромоскопия әдісін қолдануды ұсынады.

Түйінді сөздер: асқазан обыры (АО), хромоскопия, ауыр дисплазия, Жапон асқазан обыры қоғамының (JGCA) морфологиялық жіктелімі.

АННОТАЦИЯ

РЕЗУЛЬТАТЫ АДАПТАЦИИ МОРФОЛОГИЧЕСКОЙ КЛАССИФИКАЦИИ ЯПОНСКОГО ОБЩЕСТВА ПО ИЗУЧЕНИЮ РАКА ЖЕЛУДКА К КАЗАХСТАНСКОЙ ПОПУЛЯЦИИ

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Актуальность: Ежегодно в Казахстане увеличивается число заболевших раком желудка (РЖ). Так, в 2022г. выявлено 2915 человек с РЖ (15 человек на 100000 населения), занимая в структуре онкопатологии 3 место, при этом частота обнаружения ранних форм РЖ не превышает 10-20%, запущенных форм – свыше 40%; увеличивается летальность на первом году с момента установления диагноза (до 40%).

Проведение диагностики на стадии предопухолевых заболеваний желудка на начальной стадии – путь к решению проблемы ранней диагностики РЖ. Ранняя диагностика с последующей организацией лечения предопухолевых заболеваний слизистой желудка

но-кишечного тракта (атрофические, метапластические и диспластические изменения слизистой оболочки пищевода, желудка и двенадцатиперстной кишки) представляют сложнейшую проблему для онкологической службы. Для этой цели наиболее информативными в настоящее время считаются эндоскопические методы диагностики.

При этом эндоскопическое обнаружение предраковых изменений требует наличия высокотехнологического оборудования и использования методологических подходов, ориентированных на дифференциальную диагностику. Одним из методов, направленных на выявление предраковой патологии и РЖ, является метод хромоскопии.

Цель исследования – повышение эффективности ранней диагностики рака желудка путем адаптации морфологической классификации Японского общества по изучению рака желудка (JGCA) к казахстанской популяции.

Методы: Проведены эндоскопические исследования с применением метода хромоскопии у 500 резидентов РК, имеющих заболевания органов пищеварения без ранее установленного диагноза «рак желудка» и морфологические исследования биоптата, полученного при эндоскопическом исследовании, с формированием групп риска согласно JGCA (13-е и 14-е издания).

Результаты: Согласно результатам морфологического исследования полученных биоптатов 500 пациентов выявлено 3 (0,6%) случая с тяжелой дисплазией. Данная морфологическая структура отнесена к высокодифференцированной аденокарциноме. Выявленным пациентам рекомендовано оперативное лечение.

Заключение: Таким образом, выявленные случаи облигатного предрака с крайне высокой вероятностью перерождения в злокачественное новообразование доказывают важность применения JGCA для ранней диагностики РЖ и позволяют рекомендовать применение метода хромоскопии при эндоскопическом исследовании желудка.

Ключевые слова: рак желудка (РЖ), хромоскопия, тяжелая дисплазия, морфологическая классификация Японского общества по изучению рака желудка (JGCA).

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