SCREENING AS A METHOD OF EARLY EFFECTIVE DIAGNOSTICS OF GASTRIC CANCER

Tatyana Domanchuk

Higher State Educational Establishment of Ukraine "Bukovinian State Medical University"

Abstract

One of the most common forms of malignant neoplasms in the world for more than a decade is gastric cancer. It ranks 2nd in the structure of overall cancer and tends to grow steadily. According to the latest data, the WHO registers 750-850 thousand new cases of gastric cancer every year and more than 600 thousand people die from this disease [1]. Almost the only preventive method today, aimed at early detection of tumors is cancer screening. Its use helps to reduce mortality rate from certain types of malignant neoplasms including gastric cancer. Reasonability to perform screening of the population for malignant neoplasms in Ukraine today remains a matter of debate due to lack of awareness of the population and doctors, lack of clear understanding of the concept and process of screening, complexity and relatively high cost of screening methods, insufficient convincing evidence of its need for certain nosology of malignant tumors [3]. But at the same time, there is an urgent need in Ukraine to introduce a gastric cancer screening program to determine its type, as well as to substantiate its reasonability.

Key words: gastric cancer; screening; prevalence; mortality rate.

Recently the term "screening" has become stylish to use in everyday medical practice in Ukraine to denote different types of diagnostics. It is especially often used in cases to replace the concept of "early diagnosis" with a similar or identical meaning. In this sense "screening" is used for an established, indivisible, integral structure of diagnosis [2]. It is completely wrong because both are variants of phraseological units of medical examination denoting different concepts.

Screening is a mass survey of the population to identify patients or people at high risk of a disease. For many years, there have been different interpretations of screening [4]. For a clear understanding of screening, we provide two definitions that are currently the most approved in the international medical community and meet all the requirements and criteria of this process.

The problem of gastric cancer screening in our country still remains unresolved. This is due not only to the lack of adequate government funding, but also to an insufficient development of criteria specific to the region, which can identify a group of people requiring a comprehensive clinical and instrumental examination [5]. Evidence-based medical research concerning pathogenesis of gastric tumors, i.e. further progression of adenoma in adenocarcinoma provides understanding of the need for early diagnosis of gastric cancer. Screening is a systematic use of tests and procedures to identify the degree of risk and development of the disease among people who have not been consulted by a doctor concerning the symptoms of the disease. Annual screening of individuals over the age of 40 should be performed to identify risk groups for gastric cancer and subsequent dynamic endoscopic monitoring using modern endoscopic technologies that allow more detailed visualization of macroscopic changes in the gastric mucosa.

In 2018 the incidence of gastric cancer in Ukraine was estimated to be 20.9 per 100 thousand of population, which is much higher than the global total one – 11.4 per 100 thousand of population, with the incidence of gastric cancer (GC) among the male population (27, 1 per 100 thousand) significantly exceeding the identical one among women (15.5 per 100 thousand). Mortality rate due to GC in Ukraine as of 2018 was 15.3 per 100 thousand of population (among men - 20.3; women - 10.9). In the world it was 8.2 per 100 thousand of population (among men - 13.1; among women - 5.1 respectively) [1, 3, 8]. Among people who were first diagnosed with this disease, 55.5% of patients did not live in Ukraine for 1 year.

Of all the first registered cases of gastric cancer in Ukraine in 2018 only 7.5% were found during preventive examinations, which is indicative of a very low level of early diagnosis of GC.

The aim. Improve the quality of diagnosis of gastric cancer at the early stages of the disease using screening programs [4, 5].

Results. The frequency of diagnosis of stage I-II cancer is quite low - only 46.3% among those first detected. Patients who are diagnosed with stage IV disease at the time of looking for medical aid (30.8%) constitute a significant part. Only 20-30% of patients with newly diagnosed gastric cancer can undergo radical surgery. Survival of patients with localized tumors is much better than with diffuse ones. Therefore, one of the most important tasks of timely diagnosis of gastric cancer is the detection of tumors at the preclinical stages, when radical surgery is possible with minimal volume (including endoscopic resections of the gastric mucosa).

Considering the diagnosis from the side of the diagnosis, we can conclude that it is a complex pathology, the cause of which is often asymptomatic development of the disease, or the presence of symptoms corresponding to clinical manifestations of other diseases of the stomach (chronic gastritis, peptic ulcer etc.). That is why the primary task of specialists today is to find criteria for early diagnosis of gastric cancer, and using the screening method in particular.

The GC screening program, which has been operating in Japan for many years, has yielded positive results: mortality rate of this disease has 68% decreased among men and 37% among women [9]. In Ukraine in 2006 screening of gastric cancer risk groups was developed using preventive questionnaires, which took into account the history of gastric diseases. The next step should be the development of a screening system to detect precancerous conditions of precancerous changes in the gastric mucosa and early gastric cancer.

To assess the effectiveness of screening it is necessary to conduct controlled studies, preferably with randomization. A good example to apply this method is work on mammography screening for breast cancer and colon cancer using an occult blood test. The effectiveness of a particular method of screening can be pre-judged on the basis of empirical research, namely prospective (cohort) and retrospective (case-control method). Reduction in cancer mortality rate in the screening region compared to the non-screening regions may also confirm the effectiveness of the screening test. But this requires long-term population monitoring; in addition, other possible causes of reduced mortality rate must be excluded. The effectiveness of cytological screening for cervical cancer was known to be retrospectively

confirmed by comparing cancer mortality in Iceland and Finland, where mass cytological screening of the female population was conducted, and Denmark, where there was no organized cervical cancer screening program. Since the 80's there has been a gradual decline in morbidity rate. The reason for this is the change in diet and quality of food consumed, as well as the widespread introduction of gastroscopy in the 70s of the last century, which significantly improved the diagnosis of GC and precancerous diseases, which dramatically changed the structure of the disease and enabled to understand the stages of cancer development.

In 2018, 33 160 new cases of cancer of the digestive organs were detected in Ukraine, including 1,745 (5.3%) esophageal cancer, 7,503 (22.6%) gastric cancer, and 16,695 colon cancer (50, 4%), cancer of the liver and bile ducts - 2,441 (7.4%), pancreas - 4,506 (13.6%) [1].
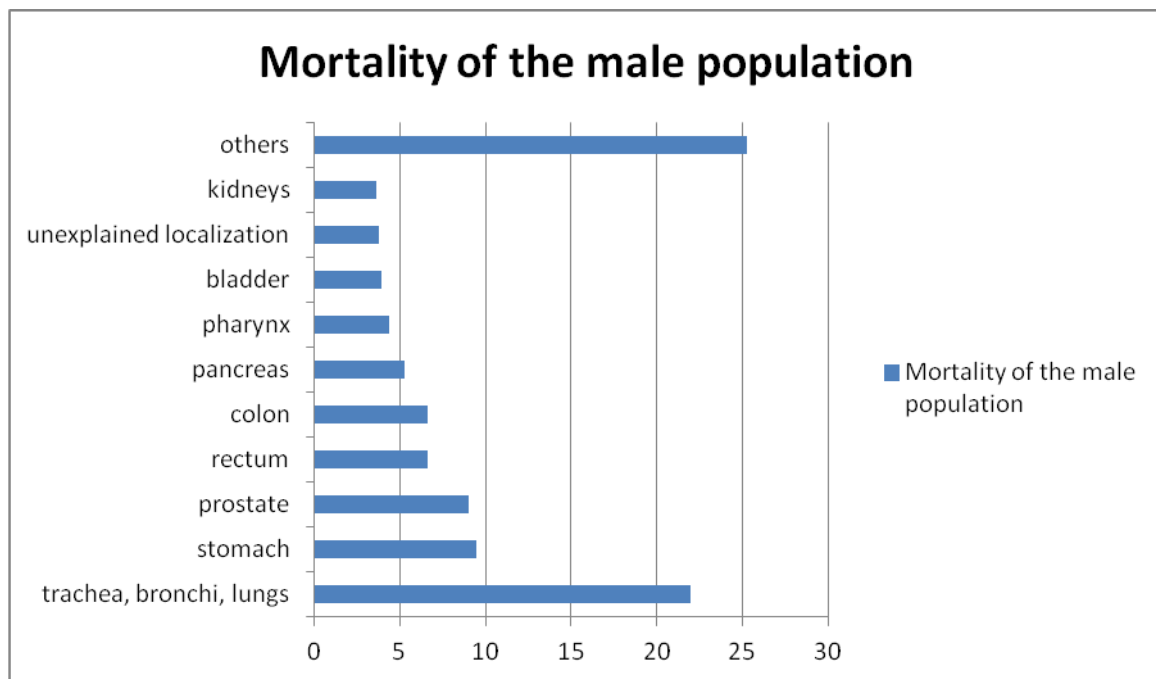
Fig. 1. Structure of mortality rate among the male population in Ukraine from malignant neoplasms in 2018

After discovery of *Helicobacter pylori* in 1982 by Marshall and Warren and its subsequent recognition as a leading etiological factor in the development of gastritis in 1994 by the International Agency for Research on Cancer (IARC), it was classified as a first-order carcinogen – an obvious carcinogen. The studies conducted have shown that the risk of cancer development in infected patients is 2-4 times higher than in uninfected ones, i.e. *H.pylori* has an obvious connection with the occurrence of cancer. This relationship is mediated by the

development of *H.pylori*-associated chronic atrophic gastritis, which plays a leading role in the pathogenic chain [12]: NORM → SUPERFICIAL gastritis → ATROPHIC gastritis → INTESTINAL metaplasia → DYSPLASIA → GASTRIC CANCER.
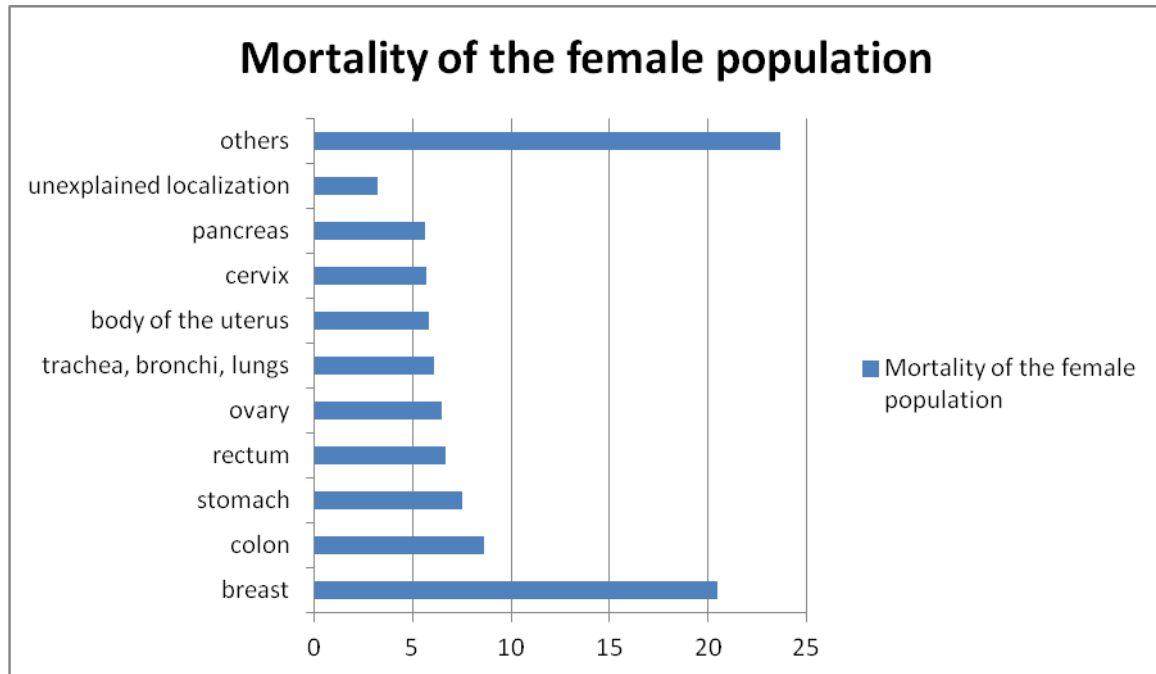

Fig. 2. Structure of mortality rate among the female population in Ukraine from malignant neoplasms in 2018

Duration of stages of gastric cancer development is quite long and lasts for 10-25 years, but with the onset of high-grade dysplasia, the risk of cancer development increases to 96% and here the time factor takes on a completely different meaning, the count goes not for years but for months, (high-grade dysplasia can grow onto cancer in 3 months). Therefore, if high-grade dysplasia is detected, second biopsy should be performed 3 months later, and the question of endoscopic mucosectomy should be considered. At the same time, despite the development of new methods of diagnostics and treatment of gastric cancer, more than 50% of tumors are diagnosed at 3-4 stages, and the 5-year survival rate in the USA and Western Europe does not exceed 5-15%. The only form of a malignant tumor of the stomach that makes it possible to achieve one hundred percent cure is early gastric cancer.

Therefore, in order to reduce mortality rate of gastric cancer, in addition to developing new regimens and approaches to treatment, early forms of the disease are obviously necessary to be found. Taking into account asymptomatic nature of the course of early gastric cancer, the only tool for its detection is screening of healthy population. Based on the data of

epidemiological studies and the APWGGC data, the optimal age for onset of gastric cancer screening is 40-45 years. Speaking about screening methods, it should be noted that today the following tools of GC screening are actively used or are being tested:

1. Photofluorography with double contrast;

2. Endoscopy;

3. Determination of serum pepsinogen 1.

Double contrast photofluorography

In Japan, the country with the highest incidence of gastric cancer in the world, 114.7 per 100 thousand of the population, 50% of the 5-year survival rate was achieved, moreover, due to the detection and successful treatment of early gastric cancer. In this country, since 1983, there has been a state program for GC screening, which made it possible to achieve such impressive results.

In 1960, gastric cancer screening started in Miayagi Prefecture using annual photofluorography with double contrasting (barium and air). The research technique consists of the following: initial ("indirect examination") consists of 8 small-frame radiographs of the stomach by the double contrast method; if any changes are found a more detailed examination ("direct examination") is performed consisting of 11 consecutive radiographs; if areas of the mucous membrane suspicious for cancer are detected, gastroscopy with biopsy is performed. In 1983, this method was completely integrated into the national health system. The population involved in the program consisted of persons over 40 years of age. By 2004, 4.4 million residents were screened, representing 13% of all the residents over 40. As a result, from 1980 to 2004, the mortality rate reduced twice as much - from 69.9 to 34.4 per 100 thousand of the population. The number of detected cases of gastric cancer was 6248, and early forms of the disease were diagnosed in 66.7% of patients. Sensitivity and specificity of double contrast photofluorography was 89% and 92%, respectively.

Nowadays, 4 cohort and 5 retrospective (case-control) studies of photofluorographic GC screening have been published. Most of the studies have shown 40-60% reduction in mortality rate of gastric cancer. Tsubono et al. (1999) conducted meta-analysis of the above studies and confirmed 49% reduction in gastric cancer mortality rate in the screening group. Sensitivity ranged within 60-80%, specificity – 80-90%.

Although survival is not a screening criterion, during meta-analysis the 5-year norm in patients identified during screening was 74-80%, and in those identified after referral it was 45-56%, which is indicative of the effectiveness of screening in detecting early forms of

gastric cancer. According to the Japanese Group for the Study of Gastric Cancer Screening, photofluorography remains the only recommended method for population-based GC.

Despite such impressive results, mass screening of gastric cancer is not performed in Europe and the USA. The reason for this, first of all, is a low incidence and high cost of such studies. Individual programs and screening programs for risk groups are more often used.

Endoscopy

Esophagogastroduodenoscopy (EFGDS) [11] is the only method that makes it possible to confirm or deny the presence of gastric cancer in a patient. With the help of high-resolution chromogastroscopy it is possible to identify the early forms of the disease and, by means of mucosectomy achieve a complete cure, that is, to stop the natural history of the development of such an aggressive form of cancer.

In Japan, high-resolution chromogastroscopy is the standard for individual screening of the population. Work on the introduction of EFGDS for breast cancer screening is being carried out both in Japan and Korea. Since 1999, the Ministry of Health of the Republic of Korea has started endoscopic screening of gastric cancer. The program involves people over 40 years old. The examination interval is 2 years. The studies conducted in Korea and Japan demonstrated a high efficiency of this method in detecting early cancers. Tashiro A. et al. (2006) conducted a comparative analysis of the effectiveness of various screening methods for detecting early cancer, and also compared the economic costs of radiological and endoscopic screening methods. With EFGDS early gastric cancer was detected in 0.87% of cases, which was 2.7 times higher than the number of early forms detected during fluorography. The cost of identifying one patient was several times lower with endoscopic screening compared to X-ray screening. However, a cornerstone for the adaptation of EFGDS for the entire population is the complexity of the study, which requires highly qualified specialists in endoscopy. Even in Japan, where the detection rate of early gastric cancer is the best in the world, the level of "missed" cases is estimated to be 19%.

Despite all the advantages of gastroscopy as a screening tool, there is not a single publication demonstrating a decrease in mortality rate among the population examined, and the sensitivity and specificity of EFGDS in gastric cancer screening are not clear. Thus, it is not possible to objectively speak about the effectiveness and advisability of endoscopic screening for gastric cancer. It is relevant to use chromogastroscopy in individual screening programs, as well as a screening tool in predetermined risk groups for gastric cancer.

Determination of serum Pepsinogen 1

Considering pathogenic relationships of atrophic gastritis and gastric cancer, screening using biochemical markers of atrophic gastritis is logical. In this regard, over the last 20 years a lot has been done to develop such biomarkers. Currently, a high correlation of histologically confirmed atrophic gastritis with the level of Pepsinogen 1 (PG1) in the blood serum and the ratio between the concentration of PG1 and PG2 has been established. The sensitivity and specificity of this method in detecting atrophic gastritis is 93% and 88%, respectively. Since 1990 in Japan serum PG marker of atrophic gastritis has been included in the GC screening programs in a test mode. The results demonstrated that this test was highly effective in detecting early cancer. In the study of 4876 healthy individuals, serological signs of atrophic gastritis after EFGDS were found in 911 individuals, cancer was confirmed in 18 cases [6].

The cumulative incidence of gastric cancer was 2.76%. Based on the survey of population of 300 000, the level of sensitivity and specificity in detecting gastric cancer was 77 and 74%, respectively (with PG1 less than 70 μg / L, the PG1 / PG2 ratio less than 3), which is a very reliable indicator for an indirect diagnostic method. However, it should be noted that this approach is acceptable only for distal gastric cancer occurring against the ground of atrophic gastritis. In case of cardiac-esophageal cancer, atrophic gastritis is not a compulsory sign and, accordingly, the effectiveness of screening by the method for determining serum PG1 will be very low.

Considering a leading role of *H. pylori* in the development of atrophic gastritis and its subsequent transformation into gastritis, Watabe et al. (2005) studied the diagnostic value of a combination of serum pepsinogen 1 and antibodies to *H. pylori* in 9293 individuals. After determining this combination of serological markers, gastroscopy was performed annually for 5 years in all the subjects [7]. Depending on the PG1 test (gastritis or not) and the level of antibodies to *H. pylori* (positive or negative test), the entire cohort was divided into 4 groups.

The results of the study demonstrated that in patients with atrophic gastritis, the risk of developing gastric cancer is 6-8 times higher than in individuals without manifestations of atrophic gastritis. Moreover, in groups with a negative test for PG1 (no atrophic gastritis), the risk of developing gastric cancer was the same regardless of the test results for *H. pylori* (positive or negative). In this work, Watabe et al. demonstrated that with the help of serological screening for PG1 and *H. pylori* antibodies, it is possible to determine a group of people constituting approximately 22%, with 70% risk of developing gastric cancer within the following 5 years. The annual incidence in this group was 0.5%. An essential term for this screening program is the possibility of annual endoscopic examination and mucosectomy of

early forms of cancer, which makes it possible to detect cancers localized within the mucous membrane and submucosal layer, and to achieve almost complete cure.

Subsequently, Oishi et al. confirmed the data of Watabe, demonstrating good predictive properties of serum PG1 in predicting the development of gastric cancer. In people with a positive serum pepsinogen test (PG1 less than 70 μg / L, PG1 / PG2 ratio less than 3), the risk of developing gastric cancer over the following 14 years 4 times increases compared with the seronegative population.

Thus, serum pepsinogen 1 is a good predictive marker for the development of gastric cancer. The use of this marker is advisable in determining the risk groups for the development of distal gastric cancer among healthy people, with the subsequent concentration of modern diagnostic and therapeutic agents on this particular part of the population to achieve the maximum effect of screening.

Conclusion

In conclusion, on the basis of the controlled studies it is necessary to state the fact that there is no evidence of the effectiveness of screening for gastric cancer. Due to the complexity and high cost gastric cancer screening is performed only in countries with a high sickness rate.

The most promising is the use of serological markers to identify population groups with a high risk of developing gastric cancer and monitor this group using modern diagnostic capabilities.

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