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Research Article

Screening for Gastric Cancer

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Abstract

Gastric cancer remains one of the most lethal types of cancer. When examining the global distribution of gastric cancer, the highest incidences are observed in South-East Asia, as well as in China and Japan [1]. Histologically, most gastric cancers are adenocarcinomas. Known risk factors are H. pylori infection, chronic gastritis, tobacco use and heavy alcohol consumption. A small percentage of gastric cancers occur hereditary. The TNM- classification is used for gastric cancer staging. Imaging methods, blood tests with tumor markers, and gastroscopy with biopsies are employed for detection, diagnosis, grading and staging. Treatment options include operation, chemotherapy, immunotherapy and radiotherapy.

There are non-invasive methods (such as H. pylori serology and plasminogen tests), invasive methods (endoscopy), and radiological methods (upper gastrointestinal series with barium, photofluorography) to screen for gastric cancer.

Screening programs are most useful for countries with high incidence of gastric cancer, where the technical and economic conditions exist at the same time. That applies to most countries in East Asia, for instance for South Korea, and of course also for Japan and increasingly for China, where the overall costs are in a favorable relationship to the benefits [2]. In countries with lower incidence of gastric cancer, non–invasive screening programs are discussed controversially, although endoscopy is readily available almost everywhere, has few complications and is affordable for most health systems. In Europe and the United States gastric cancer screening programs and recommendations regarding screening are in place in some but by far not in all countries [3].

Keywords: Gastric Cancer; Endoscopy; Screening

Introduction

Most gastric cancers occur sporadically. The aim of every examination must be to find gastric cancers at the earliest possible, curable stage. Incidence and mortality of gastric cancer are decreasing in North America and Europe, while they are still high in East Asia, Eastern Europe, Central and South America and Africa [4]. It is the fifth most common cancer and the sixth most lethal cancer type among all cancers in the world only surpassed by cancers of lung, breast, colorectum, prostate, and pancreas [5]. The age peak is globally in the 7th decade of life. Men are almost twice as likely to be affected and the 5- year- survival rate is about 33%. The first step into diagnosis is gastroscopy including biopsies, generating a clear and reliable histopathological diagnosis. Fecal tests for occult blood, molecular markers, x-ray and other tests are of secondary importance and more suitable for asymptomatic patients with corresponding risk factors [6]. The poor prognosis of advanced stages of gastric cancers and the remaining high lethality, compared to many other malignant entities, whose survival rates could be improved in the last decade, while in gastric cancer there was no noteworthy progress in establishing effective new treatment options, makes it worth to turn to other than therapeutic efforts.

At the present time it can be stated in all clarity:

The battle against gastric cancer can so far only be won by early diagnosis in surgical curable stages of the disease and through precaution and prevention.

Wealthy states all over the world would be well advised to seek success in screening programs, carried out in a consequent way and on the convincing evidence that already exists in

literature. In general, the 5 – year survival rates in gastric cancer patients are higher in Japan than in Western countries. It can be guessed that better education about the disease and the benefits of early detection, together with a screening program that exists for 4 decades could be responsible for this phenomenon in association with intensified multimodal treatment options [7,8].

Biology of gastric carcinomas

The overwhelming majority of gastric cancers are adenocarcinomas, divided into intestinal and diffuse type, mostly located at the cardia or the antrum [9]. The diffuse type is characterized by poorly differentiated cells and is associated with genetic aberrations. The intestinal type is characterized by mass lesions and due to H. pylori infections, smoking, nutritional factors and alcohol consumption [10].

Hereditary factors

3% - 5% of gastric cancers show a hereditary background and belong histologically to the group of diffuse gastric cancers. Their occurrence can be related to the Lynch syndrome, the juvenile polyposis syndrome, the Peutz – Jeghers syndrome, the familial adenomatous polyposis and less common to the Li – Fraumeni syndrome [11].

Diagnosis of gastric cancer

The leading symptoms of gastric cancers are- among few others- epigastric pain, weight loss and anemia. Early diagnosis is the only guarantee for successful treatment and outcome and is based on a series of examinations ranging from laboratory tests, radiological imaging and endoscopy with biopsies and histology to the newest immune- histochemistry methods, next generation sequencing (NGS) and PET imaging.

The use of all these methods and their significance for the respective questions differs by the current stage in the course of the disease.

Tumor markers such as CEA, CA 19-9 and CA 72-4 are frequently used as unspecific search- tests, if an occult tumor is suspected, can provide a first clue but play no undependable role in the primary approach to the diagnosis [12].

So primary diagnosis still depends mainly on gastroscopy and histology, supplemented by ultrasound and CT- scan to assess tumor stage and the presence or absence of metastasis as first steps in a rational and stage- appropriate therapy [13].

Further diagnostic modalities such as endoscopic ultrasound, for the important assessment of tumor invasion (T category) and nodal involvement (N category), laparoscopy, especially for the detection of metastasis of the peritoneum, as well as PET/CT can be used for (preoperative) staging and to plan the optimal and individualized treatment algorithm. To detect metastases in lymph nodes, in solid organs (liver) and the peritoneum, ultrasound- or CT- guided fine- needle biopsies and peritoneal cytology (by laparoscopy) can be helpful to confirm the suspicion. Positive results have a huge and unfavorable influence on the outcome and the overall survival (OS) of the patient [14-16].

In recent years, biomarkers such as HER-2-NEU, immunohistochemistry, microsatellite instability (MSI), tumor mutational burden, PD-1 and PD-L1, and neurotrophic tropomyosin-related kinase have been utilized to guide the selection of appropriate treatment options (neo-adjuvant, adjuvant, or palliative). Since a few years the liquid biopsy- technique is successfully gaining a position in tumor follow-up care and in the question of continuing chemotherapy beyond the standard schemes [17,18].

1. A short view into treatment and outcome of gastric cancer

The only curative treatment option still is surgery (gastrectomy) with lymph node dissection, increasingly used as laparoscopic procedure [19]. Radiotherapy may be important for recurrences and distant metastases in a palliative setting [20]. Chemo – (and if clearly indicated immune-) therapy is the treatment of choice for locally advanced cancers in a neo-adjuvant intention and after incomplete resected primary tumors, as well as for metastases of any stage and localization. Targeted treatments like VEGF, HER2 and PD-L1 inhibitors in the neoadjuvant setting, as well as for advanced stages are combined with chemotherapeutic protocols like FOLFIRI (Leucovorin, Fluorouracil and Irinotecan), FOLFOX (Leucovorin, Fluorouracil, Oxaliplatin) or FLOT (Fluorouracil, Leucovorin, Oxaliplatin and Docetaxel) which are the most used protocols [21-24].

Summing up, modern treatment options for gastric cancer are surgery, chemotherapy, immunotherapy and radiotherapy. For locally advanced tumors (stages T3 and T4), for tumors with a high number of loco- regional lymph nodes (stages N3 and N4) and for tumors with distant metastases (stages M), even if all available treatment options are used, the prognosis remains disappointingly bad [25].

Recently, however, certain successes have been achieved with regard to progressive- free survival through neo- adjuvant concepts and the use of new substances such as Trastuzumab or check-point- inhibitors, if indicated.

However, these achievements benefit only a small proportion of affected patients.

1.1. Surgery

Classical surgery remains the appropriate option for gastric cancer ranging from stages T1B – T4, whereas endoscopic resection is only used in the earliest stage of cancer [26]. In case of lymph node involvement best results were proved with D2 lymphadenectomy [27]. In peritoneal carcinosis HIPEC (hyperthermic intraperitoneal chemotherapy) is the option of choice. Depending on the size of the cancer in liver metastasis radiofrequency ablation or chemo

- ablation can be offered. Some studies proved good to excellent outcomes after endoscopic resection with 5 – year survival – rates ranging from 80% - 100% in gastric cancers in stage 0 [28,29]. Data proved that the 5 – year survival rate for gastrectomy and lymphadenectomy in stage I is about 70% and in stage IIB goes down to <30% [30]. Peritoneal carcinosis of gastric cancer origin has a median survival rate of 3 – 6 months but might increase up to 15 months after HIPEC in combination with cytoreductive surgery [31].

1.2. Neoadjuvant Chemotherapy

The neoadjuvant setting reduces tumor size, increases the rate of curative resection and eliminates micro- metastases. Studies proved, that neoadjuvant therapy (chemotherapy) in combination with surgery (R0 resection) provides a 5 – year survival rate of up to 36% [32].

1.3. Adjuvant Chemotherapy

Adjuvant chemotherapy has its role in cases of local or distant recurrences of gastric cancer. Limited benefits have been observed in cases of combination of chemotherapy/chemoradiotherapy with surgery. Different adjuvant chemotherapeutic regimes are combined with radiotherapy, surgery or other chemotherapeutic regimes or immunotherapy (Checkpoint Inhibitors). Some studies recently proved a median 3-years survival rate of over 50 % through chemo-radiotherapy combined with surgery [33].

1.4. Treatment of metastatic disease (palliative therapy)

The 5 – year survival rate in metastatic gastric cancer is < 10%. Median survival of patients is usually limited to 10 months. In addition to the approved chemotherapy, radiotherapy and surgery, anti – VEGF antibodies and in case of receptor- positivity, anti – HER2 – neu antibodies are used. Some studies proved that surgery plus chemotherapy/immunotherapy can prolong overall survival up to 14 months [34].

2. Screening for gastric cancer: Historical aspects of disease/cancer screening

In general effectiveness of screening is measured by reduction of mortality from any type of cancer [35]. In 1968 for the first time the criteria for disease screening were defined by Jung and Wilson for the WHO [36]. The International Agency for Cancer Research (IARC) defined in 2005 in Lyon (France), the criteria for an organized cancer screening program, which is still considered the most effective way of up-to-date cancer screening [37].

2.1. International nationwide gastric cancer screening programs

The international nationwide gastric cancer screening programs take place mainly in Asian countries, since the prevalence and incidence are much higher than in other countries all over the world [38]. For wide parts of the globe, especially Africa, no reliable data are available. In Japan and South Korea nationwide screening programs for gastric cancer are going on. In 1960 the screening program started in Japan by using photofluorography, which is replaced by endoscopic examinations nowadays [39]. In South Korea endoscopy or upper gastrointestinal series and photofluorography are used together [40]. In China opportunistic screening exists [41] and endoscopy is available free in the big cities [42]. In Singapore and Taiwan only high – risk groups are endoscopically screened [43]. Since in the United States the incidence of gastric cancer is low, endoscopic screening is not recommended, but there is an organized screening for patients with Barrett´s esophagus [44]. A specific age for gastric cancer screening does not exist, but incidence of gastric cancer increases after the age of 40. So gastric cancer screening should be recommended for countries with high incidence such as Japan and South Korea from that age on [45]. New studies in Japan prove that the incidence of gastric cancer increases the most between the age of 40 to 49 years, and so the recommended age for starting a systematic screening is for individuals of 50 years above, which is also the recommended age in many other countries, including the United States [46]. Presently- due to the poor prognosis of the advanced stages of gastric carcinomas, countries with high prevalence and mortality rates decide to fund screening programs. Because the cost-benefit-ratio of early detection is obvious, the endoscopic screening of risk groups is being discussed in the health systems of many countries around the world [47].

2.2. Costs of gastric cancer screening

Cost effectiveness of gastric cancer screening is particularly given, if there is a moderate or high prevalence of gastric cancer particularly in young patient- groups, as in the case of the aforementioned Asian countries. Nevertheless, screening for H. pylori (if positive) and eradication is cost effective also in countries with low incidence of gastric cancer, like in European countries and the United States [48].

3. Non - invasive screening methods

Gastric cancer screening can be carried out invasive and non – invasive. There is a broad field of screening options whose use is based on the criteria of the objectives, the technical possibilities (and above all- the availability of the needed endoscopic facilities) and finally the costs of the selected screening strategies [49].

Every type of screening presumably has an advantageous aspect for risk groups, but depending on the incidence and mortality of the disease (on the one hand) and economic conditions of the region that decides to roll out the program (on the other), the goals of a screening program can be very different [50].

Tumor markers, barium x-ray and conventional ultrasound, as well as CT- scan or nuclear medicine methods and even a combination of these investigations are ineffective for the detection of gastric cancers in early stages.

This sobering fact could be a starting point for creating evidence-based, clear and efficient, either nationwide or at least regional screening programs [51]. The rationale for this is less the frequency of occurrence of gastric carcinoma than the lethality of the disease [52].

As non- invasive screening methods practically only individual anamnesis, family history, recent symptoms and occult blood test in the stools remain for early detection of gastric tumors.

In most countries "screening", for these reasons is in the hands of general practitioners and the question arises, whether a first approach should be to create an evidence-based questionnaire that records the main symptoms in combination with an occult blood-stool test as a first step into screening [53].

3.1. Precursors of gastric cancer as screening tools – H. pylori

One of the main precursors of gastric cancer is H. pylori infection of the stomach mucosa. The use of H. pylori serology for the screening for gastric malignancies has a low sensitivity and neither premature lesions nor advanced tumors can be assumed by H. pylori serology, breath test or stool test alone. The only reasonable examination is the gastroscopy including the direct detection of the bacteria. On this occasion virulence factors of H. pylori such as Cag A, Vac A and Bab A may provide a valuable additional information and support the legality of eradication-therapy even in asymptomatic patients [54].

According to the Matsu Island Study in Taiwan the eradication of H. pylori decreases the incidence of peptic ulcer disease and gastric atrophy and prevents development of intestinal metaplasia and gastric cancer. The incidence was remarkably reduced by 25% [55].

3.2. Pepsinogen levels

The proenzyme of pepsin reaches the bloodstream only in a minor proportion of 1%. There are two types of pepsinogens, pepsinogen I and pepsinogen II. The levels may be low in gastric atrophy and high in inflammation. To prevent false normal results, the ratio of pepsinogen I and pepsinogen II should be considered [56]. Due to regional differences of screening, some studies use pepsinogen I levels alone, other studies use the pepsinogen I/pepsinogen II ratio. In Japan is the latex agglutination is predominant, in Europe the ELISA is favorably used. The EUROGAST study used pepsinogen I cut – off levels of < 25ng/ml. Multiple studies conducted in Japan used pepsinogen I levels < 70 ng/ml and pepsinogen I/II ratio < 3 [57]. The sensitivity for detection of atrophy (66, 7% - 84,6%) is much higher than detection of gastric cancer (36,8% - 62,3%), which means that more than 50% of gastric cancer patients are not detected or missed [58]. According to the study of Watabe, et. al. (GUT, 2005) the highest incidence of gastric cancer was associated with the risk factors for male, age greater than 60 years, severe atrophic gastritis (based on pepsinogen levels) and loss of H. pylori antibody. The annual risk for the highest risk group was approximately 2 % per year [59].

3.3. Gastrin 17

Gastrin – 17 is secreted from G – cells and reflects (comparable to low levels of pepsinogen 1) gastric atrophy. The Gastro- Panel, which is widespread used in Europe, includes pepsinogen I and II, Gastrin – 17 and H. pylori IgG – antibodies [60]. Anyway, Gastrin – 17 levels are influenced by many factors like the stomach pH, fasting or the type of food intake and although it is considered a marker for gastric atrophy, the value for cancer prediction is far too low, to be useful as a screening tool alone [61].

3.4. Tumor markers and molecular markers

The growing group of serological markers includes the actual tumor markers, genetic markers and antibodies. Tumor markers like CEA, CA 19-9, CA 72-4 to have low sensitivity and specificity and may at most be used for follow – up, assessment of therapeutic efficiency and as additional information in the individualized outcome- prediction. CEA is mostly elevated in gastric cancer stage 3 or 4 and associated with peritoneal metastases. CA 19 – 9 is elevated in advanced gastric cancer and reflects infiltration of the gastric antrum and high percentage of lymph nodes. CA 72 – 4 is elevated in relapse and reflects tumor depth, nodal involvement, peritoneal and distant metastases [62].

Micro — RNA has a proven stability in tissue, which makes it capable of becoming also a prognostic tool for the effectiveness of treatment of gastric cancer. In peritoneal carcinosis micro - RNA can be taken from the peritoneal fluid as from the ascites. For early detection the value of micro- RNA remains unclear and more research has to be conducted to verify its usefulness as a factor in a possible prediction- panel. Globally China uses the most micro – RNA as diagnostic tool for gastric cancer [63].

Last, not least the "45 – autoantibody signature panel" discriminates patients with early gastric cancer from healthy patients with a sensitivity of 43% and a specificity of 90%. The autoantibodies target tumor associated antigens for instance such as p53 tumor suppressor antigen. It is still questionable if the higher amount of autoantibodies correlate with a worse prognosis. Although this still experimental approach is rather expensive, it might be a promise for the future of non- invasive screening [64].

3.5. Volatile markers

Volatile organic compounds are divided in exogenous and endogenous compounds. Exogenous compounds are for instance smoke from cigarettes. Endogenous compounds are produced by the destruction of cells due to oxidative stress or inflammation. Gas – chromatography coupled mass – spectrometry or nano sensor technology can detect volatile particles in exhaled breath as a tool for screening for gastric cancer. Endogenous volatile gases reflect metabolic changes in the body. A nanomaterial – based gas sensor separates different volatile markers between gastric cancer patients and benign conditions with a sensitivity of 89% and 90%

specificity, but due to geographical differences, local adaptation of values is needed and the method is far from clinical use and detection of different diseases such as infectious, metabolic, genetic, cardiovascular diseases and cancer will be possible in the more distant future [65].

3.6. X – ray imaging as screening tool

X-ray of the stomach with contrast media is accurate meaningful, widely available and safe, but costly to use for large population groups. It is mainly used in countries with high incidence of gastric cancer, like China, Japan and South Korea and in countries with prosperous health systems and the necessary technology that is readily available everywhere [66].

Historically, in 1960 barium meal indirect radiograph examination was introduced in Japan [67]. Meta – analysis with 5 cohort and 2 case – control studies showed 60% to 80% sensitivity and 90% specificity [68]. Most case control studies in Japan proved a 40% to 60% reduction in mortality with photofluorography, what is the reason, that it remains being a frequently used screening tool in Japan and Korea [69]. Radiological imaging has the advantage that it is not invasive, but on the other hand the restriction, that the patients are exposed to radiation and that endoscopy is needed anyway afterwards, if there are any abnormalities found.

4. Invasive screening - endoscopy and biopsy

Endoscopy of the upper GI- tract, including biopsies of any abnormal structure of the mucosa of esophagus, stomach, duodenum or papilla of Vater defines the “gold standard” of diagnosis of malignancies in these organs, but is mainly used for symptomatic patients and patients at risk.

Despite its`s diagnostic value there are only few studies that prove the effectiveness of endoscopic screening in reduction of mortality in gastric cancer [70]. The main benefit of endoscopy is the direct visual examination of the gastric mucosa and the possibility of taking unlimited biopsy samples of any suspect mucosal area. The detection rate of precancerous or malignant lesions is high in the hands of experienced investigators [71]. Nonetheless the sensitivity of plain endoscopy is within an unsatisfying range of 78% to 84%, because especially the early cancers are not always detectable neither by visualization nor by random biopsies [72]. Advanced endoscopic imaging modalities such as chromoendoscopy and narrow – band imaging substantially helps to increase accuracy compared to the simple white light endoscopy. Chromoendoscopy uses acetic acid, indigo carmine, methylene blue, Congo-red, Lugol`s solution and other substances to identify mucosal irregularities [73]. The use of methylene blue magnification in chromoendoscopy detects intestinal metaplasia and intestinal dysplasia with sensitivities of 76% and 97% and specificities of 87% and 81% [74]. Diagnostic accuracy is increased by narrow – band imaging and digital based image enhancement technologies together with the traditional white – light endoscopy. In a sensible combination these methods can be used to examine gastric mucosa more accurate and collect biopsy samples from the suspect areas [75].

5. Screening: models and scoring systems

Some models and scoring systems for gastric cancer in low – and high – incidence countries are able to estimate the risk for development of gastric malignancies, to assess the probability of mortality and the chance of the patient on risk to survive by screening. The choice of the optimal screening strategy and -tools may be different between high- incidence countries and low incidence countries [76].

5.1. High – incidence countries

In the early 1980s Japan began the roll-out of its gastric cancer screening program with upper gastrointestinal studies using Barium. The age of screening was set with 40 years (and above) and Barium- X - ray was the only modality recommended. From 2014 on, endoscopy was implemented as an alternative primary screening option and the age of screening was raised up to 50 years with recommended screening intervals of 2 – 3 years. In 2015, as soon as the endoscopic screening program was initiated, a “microsimulation” model proved, that a 3 - year interval for patients between 50 – 75 years of age is more cost – effective. The model included demographic data like cancer incidence, mortality, survival, risk factors as smoking, alcohol consumption and the presence of H. pylori infection, which may be considered as predictors of gastric dysplasia. Of course, all these factors are changeable and therefor uncertain to estimate the progression of disease over time. The forecast of survival time and mortality risk age, sex and years after diagnosis confirmed to be valid [77]. A novel gastric cancer screening score, “Li´s scoring system” was developed 2015 and compared to the Japanese scoring system showing higher sensitivity. The Japanese scoring system includes data like age, gender, H. pylori antibody, serum pepsinogen I/II ratio and Gastrin17 levels and is divided into the categories of low -, intermediate – and high – risk. The novel Li score includes age, gender, smoking, eating salted caviar, family history and serum pepsinogen and infection with H. pylori and is also divided into low -, intermediate and high – risk groups Both systems showed a good probability of prediction [78].

The gastric cancer screening program in South Korea started at the end of the 1990s. The national gastric cancer screening program proved 20% reduction in mortality with the use of endoscopy alone. The employment condition is also included in this nationwide screening program for gastric cancer in South Korea, which consists of three models. The first model is based on adjustment for age and gender. The second model is adjusted for educational level and monthly income and model 3 includes alcohol consumption and smoking. Those three models are suitable to estimate the probability of a patient to participate in gastric cancer screening [79].

In China twice a year endoscopic screening in high-risk areas is performed. Artificial intelligence has high interest now in China and globally. A Chinese study with million images from around 84000 people proved the efficacy of artificial intelligence in gastric cancer screening. The system is called "Gastrointestinal Artificial Intelligence Diagnostic System". This model increases the accuracy and effectiveness of upper gastrointestinal tract screening, but future research and improvement are needed before it is used in organized and validated screening programs [80].

The national based cohort study from the Korean national screening program proved overall survival of 65,8% in the screened population in comparison to the non – screened population with an overall survival rate of 49,1%. Patients, who were screened 2 years the age of gastric cancer appearance had a risk reduction of 35% [81]. Proven by a case control study in Japan a 40% reduction of mortality can be reached with the use of endoscopy in organized screening programs and the five – year survival rate is 67% [82]. According to a Chinese multi - center population-based cohort study the overall survival rate is 35,7% and the risk reduction of gastric cancer in screened patients was 57% [83].

5.2. Low — incidence countries

In countries with low or intermediate incidence of gastric cancer, screening programs are developing slowly and initiatives for conducting screening programs are at least recognized as presumably useful. A cost utility study proved that the combination of upper gastrointestinal tract endoscopy and colonoscopy in patients between age of 50 and 75 years is - as expected- cost – effective for European countries with at least intermediate risk for intestinal cancers [84]. Nevertheless, gastric screening in the western world is restricted widely to patients with-high-risk gastric cancer. From this consideration, the British Society of Gastroenterology recommends performing gastric cancer screening only in patients with age > 50 years, male sex, smoking, have pernicious anemia and/ or have family history of gastric cancer [85]. According to Maastricht IV/ Florence consensus, endoscopy with biopsies is recommended in patients with family history of gastric cancer at the age of 45 years and more [86]. The Markov model used in the US proved that screening of immigrants with high – risk for gastric cancer in the United States can be cost – effective, especially in Asian Americans [87]. In the Western part of the world the incidence of the intestinal type is decreasing because of H. pylori eradication and higher food quality, while the diffuse type is increasing relatively and in some countries even in absolute numbers due to multiple factors [88].

6. Expected use of screening

The primary goal of gastric cancer screening is to detect gastric cancer in early stages of disease to improve survival [89]. A Japanese study proved that the 5 – year survival rate is 15% -30% higher in individuals screened before onset of gastric cancer symptoms [90]. Further it was shown that patients screened endoscopically 36 months before diagnosis of gastric cancer had a 30% reduction in mortality [91]. Overdiagnosis should be prevented to save extra costs and to prohibit harm to the patients. In order to rule out pointless examinations the results of which show only a weak correlation to gastric cancers in early stages and consequently produce a high number of negative results, evidence-based criteria for age and risk-factors ("target populations") have to be defined [92].

7. Screening algorithm and intervals

Some studies revealed the optimal time intervals for screening, although no guidelines exist. According to Japanese studies the 5 – years survival rate is much higher in patients performing endoscopy first 2 years before gastric cancer detection. This Japanese study and a Korean study prove that the optimal time interval would be every 2 years for endoscopic screening. But patients with gastric atrophy, intestinal metaplasia and family history should have surveillance intervals of 1 year [93]. According to a European review article a 3 – year interval endoscopic screening would be justified in patients with extensive gastric atrophy and intestinal metaplasia [94]. According to Zullo et. al. in low – risk intestinal metaplasia a surveillance interval of 2 -3 years is justified in Italy, but patients with high – risk intestinal metaplasia have a yearly surveillance as it is recommended mostly in whole Europe [95]. U.S. studies recommend an annual screening with pepsinogen levels, combined with endoscopy in patients with gastric atrophy or intestinal metaplasia, and a specific type of intestinal metaplasia in a follow – up period of every 3 years [96]. In Australia in endoscopically secured intestinal metaplasia a 1 – 3 years surveillance is recommended [97].

7.1. Screening strategies and algorithm in the United States and Asian countries

In the United States the first gastric cancer screening is recommended at the age of 50 years, especially for first and second – generation immigrants from regions such as East Asia, Russia and South America. Screening and surveillance are according to H. pylori infection status, family history of gastric cancer, intestinal metaplasia and atrophic gastritis. Hereditary gastric cancer (CDH1 mutation) and other cancer syndromes like Lynch syndrome have to be excluded. It is recommended, that individuals with relatives affected from gastric cancer should undergo endoscopic screening 10 years prior to age of the relative [98]. At the time of screening biopsies should be taken, according to the updated Sydney system. 5 untargeted biopsies are taken from which 2 biopsies are taken from the antrum, 1 biopsy from the incisura angularis and 2 further biopsies from the body. These biopsies are highly sensitive for H. pylori infections, intestinal metaplasia, atrophic gastritis and precancerous lesions [99]. Biopsies from lesions need further evaluation. If after screening the patients have no H. pylori, no family history, no atrophic gastritis and no intestinal metaplasia, no further endoscopic screening is needed. In the United States, where the incidence is lower compared to Asian countries, screening programs for immigrants from-high - risk regions and

patients with higher risk due to family history is in development and recommendations exist. For immigrants of first or second generation, high risk screening every 1 – 2 years is recommended [100]. Other countries outside of Asia, with lower incidence of gastric cancer, gain experience in screening programs to lower the mortality of gastric cancer. The development of endoscopic devices and modernization will lead to even more precise and accurate results. The-cost-effective screening model of immigrants from high – risk countries in the US should also be transferred to Europe [101, 102].

Patients with H. pylori infection need eradication therapy 6 months later confirmation of eradication and 3 – 5 years after infection another endoscopic screening. If no intestinal metaplasia or atrophic gastritis exists surveillance is stopped. If in addition to the H. pylori infection, the patient should have family history of gastric cancer or presence of intestinal metaplasia/ atrophic gastritis, endoscopic screening every 1 – 2 years is recommended [103]. Prospective studies are needed to figure out whether the survival rates of the screening protocol for gastric cancer of the United States are the same as in Korea or Japan.

7.2. Proposal for a regional screening program: Thinking about establishing a screening model

The fundamental question is: what is to be achieved and by what means? Or- in other words- how could an economical efficient screening program be structured and funded. Only as a thought experiment: For a city of two million inhabitants of whom roughly 500 000 are immigrants (in first, second or even third generation – a model that currently applies to many European cities) the goal is to develop a screening program which targets high risk groups (immigrants from high-risk countries) and those with a genetic predisposition at latest at the age of 50 and above. To figure out patients at risk for gastric cancer the cooperation of family doctors and primary health care centers is strongly demanded. A cheap and effective approach can be established in the form of simple questionnaires in all relevant languages. As soon as the data are collected and the risk- score is determined, the actual screening can begin. The most effective method (as proven above) should be endoscopy for patients in the upper third of the risk population in the end. Even if the sums for these measures seem high at the first glance, they are certainly small compared to the potential therapy costs.

Comparing the effort between prevention and treatment, including surgery and all kinds of medical therapies over a period that may span several years without curing the patient, any kind of effective screening seems to make sense.

The decisive factor should be found in a rational and realistic calculation of the cost/ benefit ratio and healthcare decision – makers need to be persuaded to establish and support a simple but effective screening.

Conclusion and Recommendations

Gastric cancer screening can be performed in non – invasive and invasive manner including contrast- enhanced X- ray and endoscopy. Gastroscopy is the method of choice for symptomatic patients and for risk – groups and should be used liberally if easily available. It`s sensitivity and specificity are far ahead of all other diagnostic methods.

For asymptomatic patients of the known risk groups, non-invasive methods such as H. pylori testing, or pepsinogen levels might be helpful in early recognition of the development of gastritis into intestinal metaplasia or atrophy as pre- cancerous conditions and precursors of a further progression into gastric cancer. This kind of screening may be considered for countries with low incidence, but is not sufficient for those with a high incidence of gastric cancer. Invasive screening has been demonstrated to be useful and cost - effective in countries with a high incidence of gastric cancer, especially in younger population groups as is true for Japan and Korea. Endoscopic methods have the benefit, that radiation can be avoided and the complication rate is extremely low for diagnostic use only.

Depending on the screening regulation of every country, mostly in high incidence regions with large population numbers such as in East Asian countries, non – invasive methods in combination with X-ray are used for screening at different time intervals. In China “artificial intelligence” is tested for gastric cancer screening and showed promising first results, but still needs to be improved before being implemented in organized screening programs. Widespread and methodically applied screening programs promise to be the right way to increase the 5 – year survival rate of gastric cancer in the long run. In the next future it will be important to screen individuals with a high risk for gastric cancer consequently but at the same time to use the available resources as sparingly and precisely as possible in order to generate the greatest achievable benefit for patients at risk and- at the same time- for a country`s economy. The only cure for gastric cancer still is surgery with or without chemotherapy and immune- therapy. In advanced stages all therapy modalities can prolong survival only minimally and in general, the outcome, depending on the stage, is still poor in metastatic disease [104].

Further prospective studies are needed to develop successful screening models in terms of cancer prevention and outcome optimization for patients on risk and therefore, prevent human suffering resulting from a fatal, but curable disease in its early stages. The decisive fact has to be found in a rational and realistic calculation of the cost/ benefit ratio. The goals of effective screening are anything but trivial. It is important to prevent avoidable cases of advanced disease and at the same time to realize an economic benefit. Uniting these goals will be an essential but achievable strategic health task in the coming years.

National and international guidelines that are based on epidemiological data and stand up to objective examinations regarding all the above listed criteria are most desirable.

Screening tool	Advantage	Disadvantage	Limitations
H. pylori screening	Prevention of developing gastric cancer, not invasive	Low sensitivity, precancerous lesions can´t be detected, breath test is expensive	Impractical application
Pepsinogen levels	High sensitivity for detection of gastric atrophy	Low sensitivity for gastric cancer detection	Hardly available in practice
Gastrin 17	Sensitivity for gastric atrophy	Low sensitivity for gastric cancer detection	Influenced by eating, stomach pH etc.
Molecular markers + Tu - markers	Useable for follow – up, therapy assessment and prediction. Micro - RNA: prognostic marker and treatment efficiency 45 – autoantibody panel: Discrimination of patients with early gastric cancer from healthy individuals.	Tumor markers: Low sensitivity for gastric cancer detection. Micro - RNA: further research has to be conducted and prediction still unclear and expensive. 45 – autoantibody panel: expensive and still in trial and expensive	Unspecific, difficult interpretation positive in infections or inflammation - processes.
Volatile markers	Distinguish early gastric cancer from healthy individuals. High sensitivity and specificity	Still experimental, expensive	Not useable in practice
X – ray examination	Cheap and fast	Radioactive exposure, low sensitivity and specificity	Has to be confirmed by endoscopy
Endoscopy and biopsy	High sensitivity and specificity, precancerous and cancerous lesions detectable	Invasive and high costs	Early cancers sometimes missed

Table 1: Summary of all screening methods with advantages, disadvantages and limitations.

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