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Εθνικόν και Καποδιστριακόν Πανεπιστήμιον Αθηνών

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ΙΑΤΡΙΚΗ ΣΧΟΛΗ

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"THE INCIDENCE OF GASTRIC CANCER IN THE POPULATION, THE AVAILABLE THERAPIES AND THE NEED FOR NEW INNOVATIVE THERAPIES; A LITERATURE REVIEW"

Ονοματεπώνυμο: Μαγδαληνή Κουκότσικα

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Ιδιότητα: Φαρμακοποιός

Επιβλέπων: Φλώρα Ζαγουρή, Παθολόγος Ογκολόγος, Καθηγήτρια Θεραπευτικής Κλινικής Ιατρικής Σχολής ΕΚΠΑ

Αθήνα, 2024

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PREFACE

This Thesis is the culmination of the postgraduate programme "Clinical Trials: Design and Conduct", of the Medical School of the National and Kapodistrian University of Athens. Under the guidance of Professor Flora Zagouri, a very interesting and exciting journey in the scientific field of design and execution of clinical studies in medical science has been completed.

This Master Thesis presents some of the recent literature data on gastric cancer, its incidence in the general population, the currently available treatment options and the possible targets for the future - innovative therapeutic interventions. I would like to thank all the scientific staff and the lecturers of the postgraduate programme for their unreserved help throughout my studies.

Above all, I would like to thank my family for their support and patience throughout my studies, cause without their help I would not have been able to complete this postgraduate programme.

This Thesis is devoted to my beloved Dad, who did not make it to be here today, as he was defeated by this horrible disease, despite all possible treatments that he went through for 2 consecutive years. He fought so hard and so strong for 2 years, as a Real Hero, who is always next to us and he would be so proud for all the efforts I put to finish this Master degree, but unfortunately no current treatment or medical knowledge could help him and save him. I feel very disappointed that despite we live in the 21st century, science cannot defeat cancer and I really hope that the future innovative therapeutic interventions will arise with the personalized treatments to conquer the main therapeutic option.

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Περίληψη

Τις τελευταίες δεκαετίες η επίπτωση του γαστρικού καρκίνου παρουσιάζει σταθερή μείωση, ιδίως σε πληθυσμούς όπως οι ΗΠΑ, ο Καναδάς και αρκετές ευρωπαϊκές χώρες, λόγω της συνεχιζόμενης προσπάθειας για την εξάλειψη του Helicobacter pylori, το οποίο αποτελεί σημαντικό συστατικό της παθοφυσιολογίας του γαστρικού καρκίνου. Για την επίτευξη της εξάλειψης του κινδύνου εμφάνισης γαστρικού καρκίνου έχουν υιοθετηθεί τόσο μέτρα πρωτογενούς όσο και δευτερογενούς πρόληψης, συμπεριλαμβανομένων της βελτίωσης της διατήρησης των τροφίμων, της προσωπικής υγιεινής και των διατροφικών συνηθειών και της έγκαιρης ανίχνευσης μέσω ενδοσκοπικών μεθόδων αντίστοιχα. Ωστόσο, απέχει πολύ από το να καταστεί ένας σπάνιος τύπος καρκίνου, με μεγάλη διακύμανση όσον αφορά τη συχνότητα εμφάνισης παγκοσμίως και με τα ποσοστά σε αρκετές χώρες να εξακολουθούν να παρουσιάζουν αυξητική τάση.

Σκοπός της παρούσας διατριβής είναι να συγκεντρώσει επιδημιολογικά δεδομένα από διάφορες μελέτες για τον καρκίνο του στομάχου και να εξετάσει τα βασικά σημεία των διαθέσιμων σήμερα θεραπειών καθώς και τις μελλοντικές προοπτικές που θα μπορούσαν να εξασφαλίσουν χαμηλότερη θνησιμότητα και καλύτερα ποσοστά επιβίωσης για αυτή την πολύ σοβαρή νόσο.

Οι αναθεωρημένες κατευθυντήριες οδηγίες κλινικής πρακτικής για τη θεραπεία του καρκίνου του στομάχου, που δημοσιεύθηκαν από το Εθνικό Ολοκληρωμένο Δίκτυο για τον Καρκίνο (NCCN) το 2022, δίνουν ιδιαίτερη προσοχή στη διεπιστημονική αντιμετώπιση της νόσου με τη συνεργασία επιστημόνων από διαφορετικούς κλάδους, προκειμένου να επιτευχθεί το καλύτερο δυνατό αποτέλεσμα για τον ασθενή. Με τη συνεχή ανάπτυξη της επιστημονικής έρευνας στον τομέα αυτό, τα τελευταία χρόνια οι στοχευμένες (targeted) θεραπευτικές παρεμβάσεις έχουν δώσει νέες ελπίδες στην προσπάθεια αντιμετώπισης του προχωρημένου γαστρικού καρκίνου.

Λέξεις – κλειδιά: Καρκίνος του στομάχου, Επιδημιολογία, Θεραπεία

Abstract

During the recent decades gastric cancer's incidence has demonstrated a steady decline, especially in populations like the US, Canada and several European countries, on account of the ongoing effort for eradication of Helicobacter pylori which is an important component of the pathophysiology of gastric cancer. Both primary and secondary prevention measures have been adopted towards the achievement of gastric cancer risk elimination, including improved food preservation, personal hygiene and dietary habits and early detection via endoscopic methods respectively. However, it is far from becoming a rare type of cancer, with a high variation in terms of incidence worldwide and with the rates in several countries still experiencing an increasing trend.

The aim of the present thesis is to gather epidemiological data from various studies covering all geographically distinct components of the global rates for gastric cancer and to address the key points of the currently available therapies as well as the future perspectives that could assure a lower mortality and better survival rates for this deathly malignancy.

The revised clinical practice guidelines for the treatment of gastric cancer, published by the National Comprehensive Cancer Network (NCCN) in 2022 pay particular attention to the multidisciplinary treatment of the disease with the cooperation of scientists from different disciplines in order to achieve the best possible outcome for the patient. With the continuous development of scientific research in this field, in recent years targeted therapeutic interventions have given new hope in the effort to treat advanced gastric cancer.

Key – words: Gastric, Cancer, Epidemiology, Therapies

Introduction

During the recent decades gastric cancer's incidence has demonstrated a steady decline, especially in populations like the US, Canada and several European countries, on account of the ongoing effort for eradication of Helicobacter pylori which is an important component of the pathophysiology of gastric cancer. Both primary and secondary prevention measures have been adopted towards the achievement of gastric cancer risk elimination, including improved food preservation, personal hygiene and dietary habits and early detection via endoscopic methods respectively. However, it is far from becoming a rare type of cancer, with a high variation in terms of incidence worldwide and with the rates in several countries still experiencing an increasing trend.

The aim of this thesis is to gather epidemiological data from various studies covering all geographically distinct components of the global rates for gastric cancer and to address the key points of the currently available therapies as well as the future perspectives that could assure a lower mortality and better survival rates for this deathly malignancy.

In the first section, epidemiological studies are cited and data concerning the incidence and mortality of gastric malignancy throughout the globe are analyzed. What needs to be noted here is the substantial variability in terms of incidence in different continents and countries as well as the confirmed decline in the global trends of incidence and mortality. Nevertheless, the case fatality rate for gastric cancer approaches 75% worldwide, rendering it one of the most important contributors to the global disability- adjusted life-year burden.

In the second segment, current application of treatment strategies is discussed, with the available and emerging targets aiming at maintaining the 5-year survival rates as high as possible especially for early-stage cancer (IA, IB). When taking into consideration the stage of disease and the detection of several biomarkers, treatment options include surgical intervention, cytotoxic therapies (neoadjuvant or adjuvant chemotherapy) and targeted therapies like Tyrosine Kinase Inhibitors, Cell Structure Remodeling therapies and Immunotherapy.

In the third and final section of this study, novel therapeutic strategies and future perspectives are addressed, with a special interest in tumor microenvironment (cancer associated fibroblasts, immune modulation, angiogenesis) and biomarkers like micro-RNAs and autophagy mediators. Gut microbiome targeted-therapies are also in the spotlight since patients with gastric cancer bare provably different populations of gut microbiota, especially when it comes to bacterial

pathogen growth in the stomach, emphasizing on the potential benefit of the use of probiotics. Most advances in the field of innovative therapies are based on the understanding of the molecular pathways and the molecular classification for gastric cancer that has recently arisen.

A. Chapter 1. Gastric cancer

A.1 Stomach physiology

The stomach is a major component of the upper digestive track, located between the esophagus and the small intestine and responsible for the digestion of food via secretion of several enzymes and fundamentally gastric (hydrochloric-HCl) acid. There are 5 distinguishable topographic regions in the stomach: the cardia, the gastroesophageal junction, the fundus and the corpus which contain acid-secreting glands (HCl-secreting parietal cells) and the antrum and the pylorus which contains gastrin-secreting G-cells and is lined with an epithelium that secretes alkali. The mucous membrane that lines the stomach is composed of columnar epithelium that encapsulates the glands and the different types of cells. Several regulatory hormones are secreted by the gastric glands, like gastrin which promotes gastric acid secretion via stimulation of histamine release by the enterochromaffin-like cells which in turn induces the production of HCl by the parietal cells. (Another hormone secreted by the D cells of the stomach that acts antagonistically to gastrin is somatostatin.) [1]

Gastritis- Cancerization

Hypergastrinemia is a condition that may arise as a response to gastric hypochlorhydria resulting from chronic atrophic gastritis that is provoked by Helicobacter pylori (H. pylori) and is linked to the formation of gastric tumors. Chronic mucosal inflammation provoked by H. pylori leads to a gradual loss of gastric glands- mucosal desertification- and finally atrophy which is subsequently accompanied by intestinal metaplasia (replacement of the natural glands by inappropriate ones, prone to further derangement of their structure and molecular instability) which eventually evolves into intestinal-type gastric adenocarcinoma. [2] The process of cancerous formation is a prolonged one, with distinct, consecutive stages known as the Correa cascade: chronic inflammatory changes resulting from active gastritis lead to chronic atrophic gastritis, followed by intestinal metaplasia and then dysplasia (intraepithelial neoplasia) and eventually carcinoma. The process is also multifocal, beginning from the incisura angularis and then spreading to the entire stomach walls. [3] In the majority of cases gastric cancer presents as adenocarcinoma (95%), with the second most frequent type being primary gastric lymphoma.

A.2 Classification

In terms of topography, gastric cancer is classified as being either cardia (near the gastroesophageal junction) or non-cardia/distal cancer. The two types bare epidemiologically

distinct patterns, with tumors situated in the cardia increasing in frequency in developed countries and displaying a more aggressive behavior. Depending on the degree of invasion, we can distinguish between early and advanced tumors with the first being limited to the mucosa and submucosa and having better survival rates than the second ones. [3] From a histological point of view, the Lauren classification is widely used to classify gastric malignancy into 2 categories, the intestinal and the diffuse type, with the first one displaying intercellular junctions, glandular formation and cellular cohesion, while the second one shows no intercellular junctions and poor cohesion between cells. There is also a third type, the indeterminate one, to include uncommon histology.[4] The most commonly encountered is the intestinal type, occurring more frequently among men of older age, while the diffuse type concerns mostly women of younger ages and is related with a worse prognosis. [5] Another important classification system is that of WHO which entails all subtypes of gastric cancer even the infrequent ones, with corresponding categories to these of the Lauren classification, like tubular (the most frequent type), mucinous and papillary adenocarcinoma which are subtypes of the intestinal type, signet-ring cell and other carcinomas with poor cell cohesion which fall into the category of diffuse and finally mixed and adeno-squamous or squamous cell carcinomas which are basically analogous to the indeterminate category. [6] Furthermore, based on the age at the diagnosis, gastric cancer is categorized as early-onset or conventional when the patient is less or more than 45 years old at the diagnosis respectively. Early-onset cancer is probably more influenced by genetic factors than environmental carcinogens, with around 10% of these cases having a positive family history. [7] A special subtype of gastric malignancy is gastric stump cancer that is localized at the remainder of the stomach after partial gastrectomy most often in the setting of gastritis and ulcer that is brought about by H. pylori. [8]

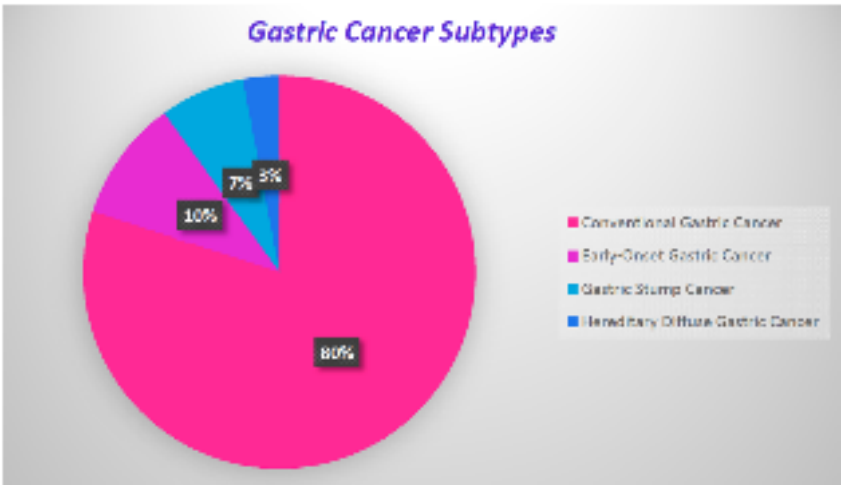

Figure 1: Gastric cancer subtypes

Source: Machlowska et al., (2020)

A.3 Etiology/Risk Factors

Major risk factors that constitute a crucial part of the development of gastric carcinoma are: genetics/ family history, dietary habits, alcohol consumption, smoking and Helicobacter pylori and EBV infection. Genetic factors contribute a mere 1-3% in the total of all cases of gastric malignancy, since the majority are sporadic and about 10% are hereditary. The best described type of familial gastric cancer is Hereditary Diffuse Gastric Cancer (HDGC) which is induced by loss of one copy of cadherin-1 gene (CDH-1) and has an autosomal dominant inheritance pattern. Other syndromes that are linked to gastric cancer include Lynch syndrome, Familial Adenomatous Polyposis (FAP) syndrome and Gastric carcinoma and proximal polyposis of the stomach. [9] The impact of dietary habits on gastric cancer has been thoroughly researched by the World Cancer Research Fund/ American Institute for cancer Research concluding that fruits and vegetables act in a protective manner to prevent gastric cancer formation while red – processed meat, salt- preserved and smoked foods promote cancer development. Nitrates and nitrites, like NMDA, used as food additives in meat, act as potential carcinogens, A high intake of salt brings about disruptions of the gastric mucosal barrier, causing inflammation and therefore increasing the risk for malignancy by 68% compared to low salt intake. [10] Furthermore, heavy alcohol intake has been found to confer an augmentation in the risk for both

types of gastric malignancy, cardia and non-cardia. [11] Another risk factor that predisposes to the formation of carcinomatous lesions in the stomach, especially in males and non-Asians is obesity, because of inflammation inducement. The causal relationship between gastric cancer and smoking has been elucidated recently as a meta-analysis has demonstrated a 1,53-fold increase in the risk of carcinogenesis in the stomach. [12]

Helicobacter pylori is a gram negative bacterium that has been recognized and identified as a class I carcinogen as far as gastric cancer in concerned by the WHO as early as 1994. In the majority of H. Pylori positive cases, individuals get infected during childhood and the infection remains throughout life. The long-term effect of H. pylori infection is consistent with the structural and functional changes of chronic gastritis navigating from an inflammatory stage to its atrophic counterpart, inducing epithelial-to-mesenchymal transition and preneoplastic changes, thus leading to the development of gastric cancer. Notably, the bacterium accounts for 90% of all cases of non-cardia gastric malignancy with the rates of gastric cancer being in direct correlation with the bacterial infection's prevalence. [13] Apart from the inflammatory reaction, H. Pylori also yields a direct epigenetic effect on epithelial cells of the stomach, with vacA and cagA positive strains bringing about a higher risk for malignancy. [14] Although H. pylori is inextricably linked to gastric cancer, it appears to have a protective role against gastro-esophageal reflux disease and esophageal/ cardia adenocarcinoma. Subsequently, H. pylori eradication may have successfully decreased the frequency of non-cardia cancer but it has led to a simultaneous augmentation in the incidence of its counterpart, cardia cancer. On the other hand malignancies of the gastric cardia share the same risk factors as esophageal ones like obesity and gastroesophageal reflux disease complicated by Barrett esophagus. [15] H. pylori detection is achieved via upper gastrointestinal tract endoscopy with biopsy sampling (a minimum of 2 biopsies from the antrum at the level of the large curvature, 1 from the small curvature and 2 from the fundus) for histopathological characterization, cultures/ PCR and rapid-urease test, all of which can help us grade the level of inflammation, metaplasia or dysplasia of the gastric mucosa and thus stratify the risk of malignancy.

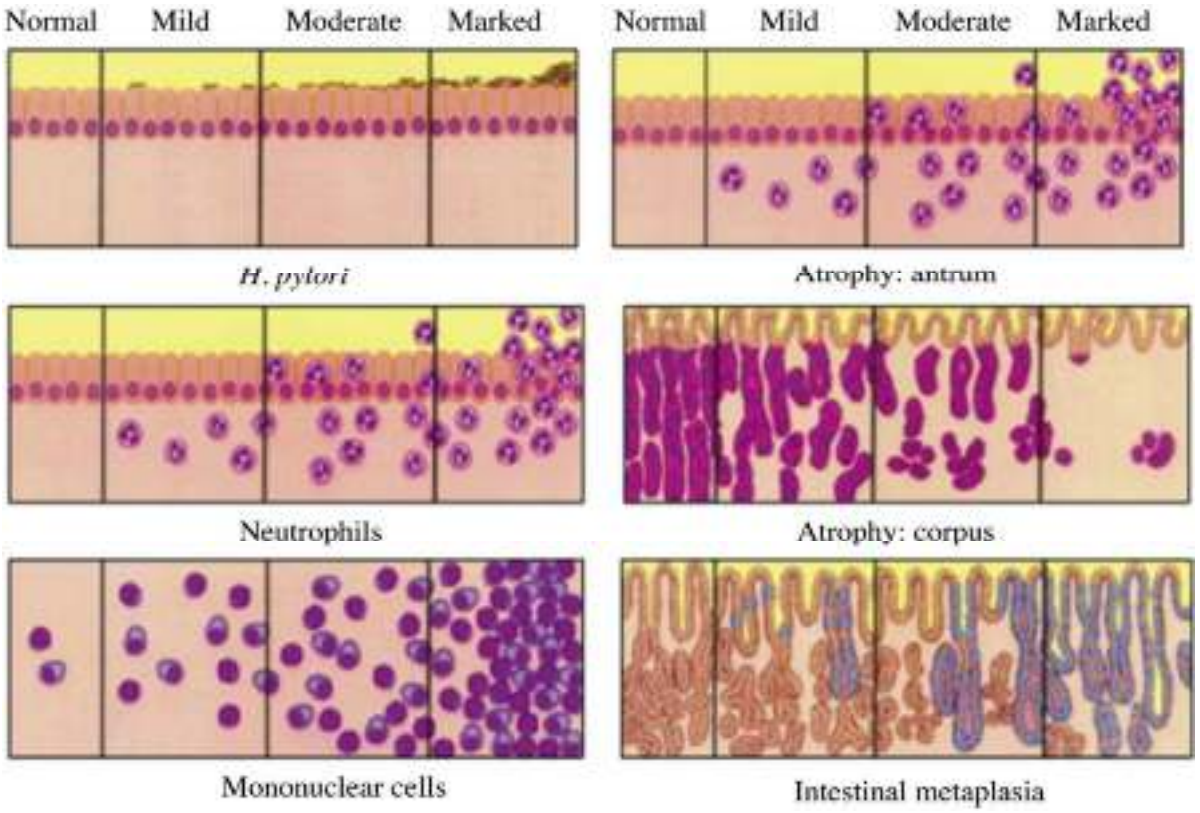

Figure 2: The Sydney Classification for gastric lesions

0 for normal, 1 for mild, 2 for moderate, 3 for marked modifications relating infiltration by inflammatory cells like neutrophils or mononuclear cells, severity of the atrophy of the corpus and significance of intestinal metaplasia.

Another infectious factor that has been associated with gastric cancer is Epstein- Barr virus (EBV), with 5-10% of all cases being associated with EBV genome, especially the ones situated in the gastric cardia or occurring post-surgically, although the exact role of the virus has not yet been elucidated. [16] Non Steroidal Anti-inflammatory Drugs (NSAIDs) along with aspirin seem to lower the risk for gastric cancer (non-cardia type) by up to 22% according to a recent study and statins (anti-hyperlipidemic drugs) also seem to act as chemoprotective drugs for gastric cancer. [17]

With regard to sex as a predisposing factor for gastric malignancy, female estrogens seem to exert a protective effect on women since men are 2 times more frequently affected by this type of cancer than women. [18] Socioeconomic status also plays a role probably because of H. pylori being more frequently encountered and fresh food being less accessible, with lower socioeconomic groups baring a higher risk for gastric cancer.

A.4 Epidemiology

On general terms, cancer is a developmental process forged under the influence of both genetic and environmental factors that exert their damaging effect in the course of several decades before progressing to the tumor formation. Gastric malignancy is deemed a multifactorial entity with a global burden, being the fifth most frequently diagnosed cancer worldwide and the third leading cause of death that is caused by cancer. [19] The number one new cases of gastric that were reported in 2018 exceeded a million according to the GLOBOCAN which made an estimation of approximately 800.000 deaths on a global scale, rendering this type of malignancy the cause of 8,2% of all deaths from cancer in 2018. The average incidence rate for gastric cancer is 3 times higher among developed nations compared to low-middle Human Development Index nations. [18] Until 1980 gastric malignancy was ranked first in terms of cancer- related mortality globally, only to be surpassed by lung cancer, partially because of a decrease in the incidence and mortality of the former. Indeed a steady decline of incidence rates has been observed during the recent years in gastric cancer especially in areas with historically high rates of this specific type of cancer like Japan and Korea, thus putting gastric cancer in the sixth place of the most common malignancies in the global ranking in 2020 according to the more recent GLOBOCAN estimates. [18]

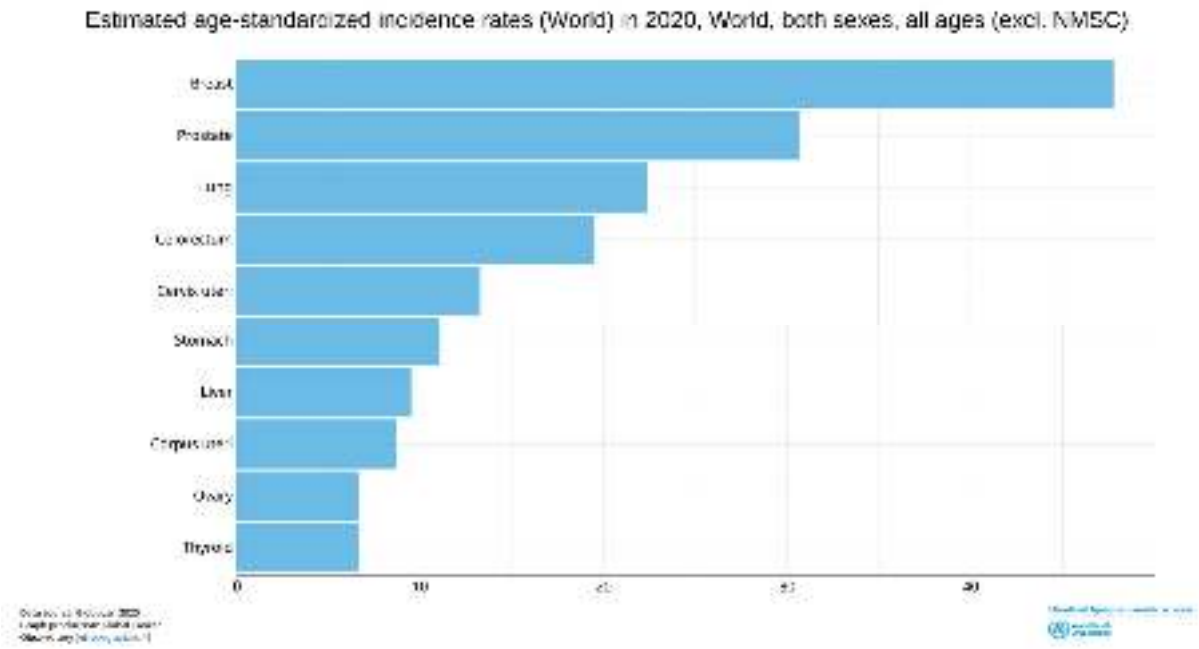

Figure 3: Estimated age-standardized incidence rates (World) in 2020

World, males, all ages From GLOBOCAN 2020; Graph production: IARC (http://gco.iarc.fr/today) World Health Organization.

Gender wise, the cumulative risk for gastric cancer development until the age of 74 has been calculated up to 1,87% in male individuals and 0,79% in female individuals. It is evident that gastric cancer rates are higher in males, being 2,2 times and 1,83 times more frequent in males than females in developed and developing countries respectively. [12] Based on the differences that are observed because of sex, gastric cancer ranks as the fourth most commonly observed type of cancer in men and the seventh most commonly observed type of cancer in women. The lifetime risk for gastric malignancy ranges from 1 in 54 men to 1 in 126 women. [18]

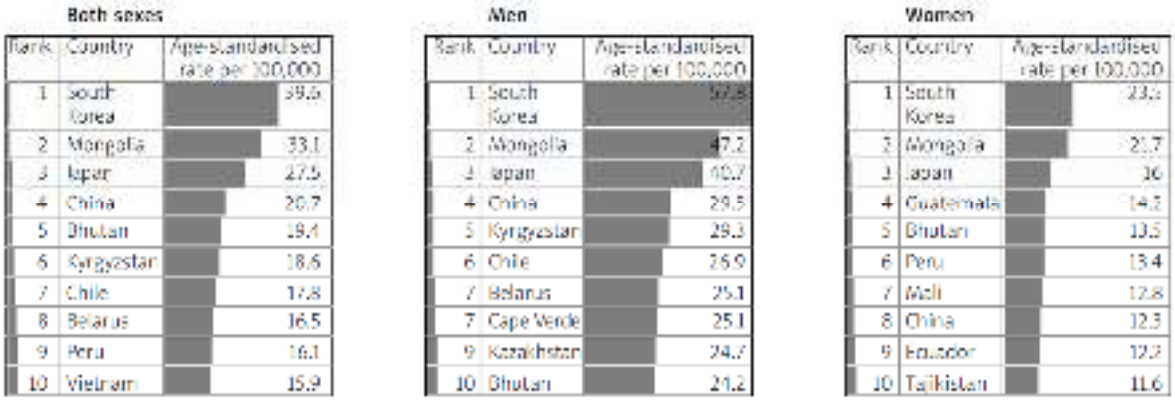

Figure 4: Age-standardized incidence estimates per 100.000 for stomach cancer in 2018, for all ages and both sexes

Source: P. Rawla 2019/ GLOBOCAN 2018

Gastric cancer mainly affects older individuals, with a mean age at the diagnosis ranging from 55 to 80 years old. It is rarely encountered among adults younger than 45 years old in which case genetic factors play a more important role than environmental ones. [20] Regarding topography, the epidemiology differs in that cardia gastric cancer occurs more frequently in countries of central Asia, while non-cardia gastric cancer is found more often in countries of Eastern and South-eastern Asia. Despite the downward trend in the rates of non-cardia cancer on grounds of H. pylori eradication, it is still the most commonly diagnosed type of gastric cancer, with 8,8 per 100.000 persons versus 3,3 per 100.000 persons for cardia cancer in 2012. In fact the ratio of non-cardia to cardia gastric cancer is 40 to 1 in the region of sub-Saharan

Africa for men. On the other hand in Northern America and Oceania it the same ratio is 1 to 1 for men and almost 2 to 1 for women. One of the countries where cardia and non-cardia cancer incidence appear in a reverse mode is the UK, where cardia gastric cancer is observed 1,5 times more frequently than non-cardia cancer in men and in similar rates in women. [21]

The epidemiology of gastric cancer seems to follow that of H. Pylori and consequently all changes in the epidemiological patterns of the bacterium are depicted in the global trend of gastric cancer diagnosis. During the 19th century the prevalence of H. Pylori increased because of crowded living conditions and poor hygiene and afterwards it diminished during the 20th century on grounds of an amelioration of the aforementioned factors. [22] According to a review and meta-analysis by Hooi et al of studies exploring the prevalence of H. Pylori between 1970 and 2016, it was deduced that more than half of the population was infected with the bacterium globally. The regions with the highest prevalence were Africa, followed by Latin America and Asia and the lowest prevalence was observed in Oceania and Northern America, but after the advent of the 21st century a decline in the rates of H. Pylori was observed in the industrialized world, as in Northern America and Europe. [23] The continuing efforts for H. pylori eradication in developed countries via prevention and treatment has led to a significant fall in the prevalence of gastritis, ergo it has diminished the evolution to carcinomatous lesions in the long-term. Hence, prevalence of H. Pylori during 2015 was calculated up to 79,1% in Africa, 63,4% in Latin America and the Caribbean, 54,7% in Asia and at the lowest end of the spectrum there is Northern America with 37,1% and Oceania with 24,4%. Variations can be observed between different countries, but also on a racial level regardless of the country. For instance, the frequency of H. Pylori infection in the USA in non-whites ranges from 34,5% to 61,6%, while in non-Hispanic whites it is much lower, around 18,4-26,2%. [24] The reported fall in gastric cancer rates in countries like Japan is indicative of the attempts to prevent and treat H. Pylori infection, since the predicted prevalence in a meta-regression analysis fell from 34,9% in 1970 to 6,6% in 2000. [25] More recent data from 2017 showcase low rates of H. Pylori in school children, up to a mere 3,1%. [26] Prevalence patterns in many countries depend on the migratory flows, since it has been demonstrated that migrants most usually preserve prevalence rates that are reflective of their country of origin and are more often than not higher than these of their country of destination. [27]

In spite of the acclaimed implication of H. Pylori infection in the pathogenesis of gastric malignancy, the epidemiological patterns of the two entities do not entirely coincide. The reason for that is the predominance of different strains of the bacterium in the various countries where

it thrives, with some strains being more virulent and carcinogenic than others. To be more specific, East Asia and the Colombian Andes are the countries with the highest percentages of cagA (cytotoxin associated gene) positivity, which encodes an oncogenic protein that is linked to an elevated risk for non-cardia cancer. Another virulence factor that causes epigenetic changes on gastric cells and leads to premalignant lesions is vacA. On the other hand, African H. Pylori strains are mostly cagA-negative leading to a non-atrophic gastritis pattern that does not promote gastric cancer formation. [28] [29] It is currently understood that genetic alterations throughout the years have led to the circulation of different prototypes of the bacterium including hpEurope, hpAfrica1, hpAfrica2 and hpSahul (in Oceania). European strains have been incriminated for the formation of premalignant lesions to a higher extent than other strains. [3]

With reference to the geographical variation of gastric malignancy's incidence, the peak rates have been noted in countries of Eastern Asia (32,1/13,2 per 100.000 men/women respectively), followed by central and Eastern Europe (17,1/7,5 per 100.000 men/women respectively), South America (12,7/6,9 per 100.000 men/women), while the lowest rates are noted in Northern America (5,6/2,8 per 100.000 men/women) and Africa (5/3-4 per 100.000 men/women). Overall more than 60% of all gastric malignancies were detected in Eastern and South-Eastern Asia in 2018. [30] The highest and lowest cumulative risks of gastric cancer were spotted in Eastern Asia (2,64%) and in Southern Africa (0,42%) respectively. [31]

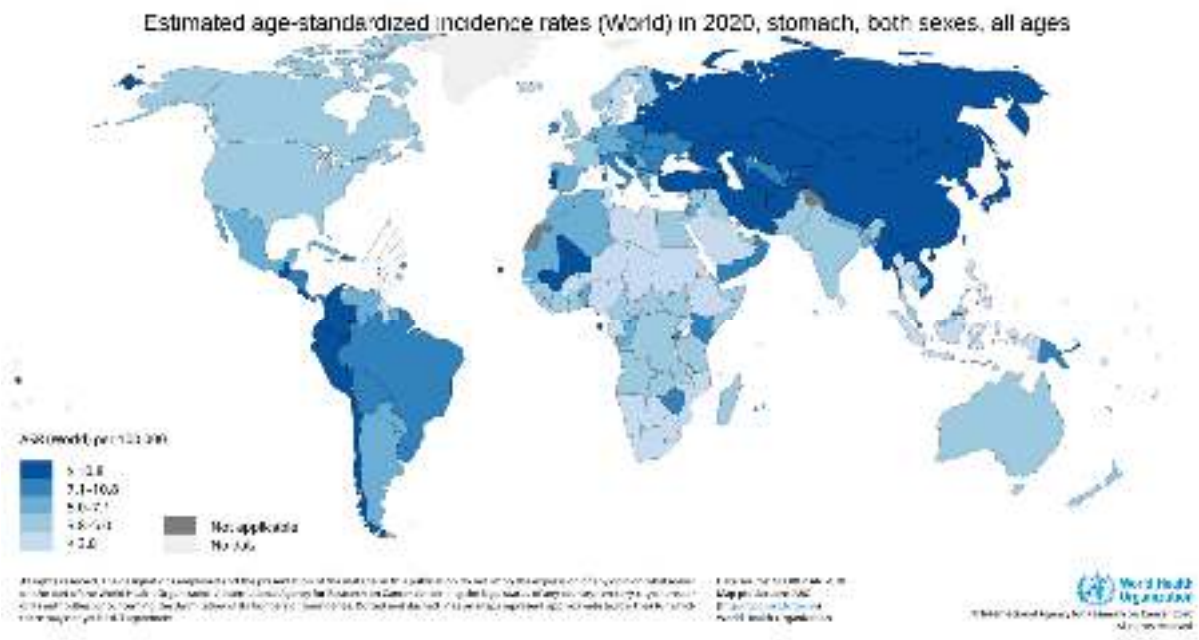

Figure 5: Age- standardized incidence rates per 100.000 for gastric malignancy in 2018

Source: GLOBOCAN 2018 (http://gco.iarc.fr/today) World Health Organization

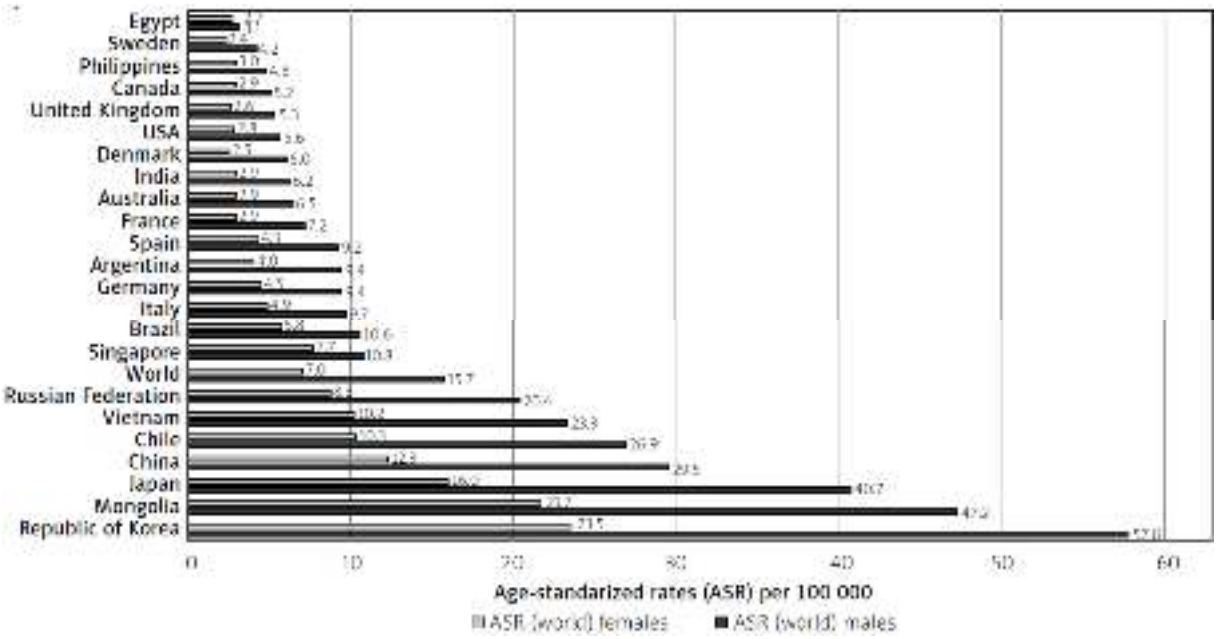

Figure 6: Estimated age-standardized incidence rates for gastric cancer in 2018, for both males and females, globally

Source: GLOBOCAN 2018 (http://gco.iarc.fr/today)

More specifically, in the US gastric cancer incidence rates have drastically changed in the past decades presenting a notable decline from 11,7 per 100.000 in 1975 to 6,6 per 100.000 in 2017. According to the United States Cancer Statistics (USCS) registry, during the period 2001-2015 there was an important decrease of the incidence rates for gastric malignancy, by 0,94% per year. [32] Despite the decline in the incidence of non-cardia cancer in the US, the incidence of cardia cancer among people who are younger than 50 years old seems to augment. The estimated lifetime risk for gastric cancer in the US is around 1 in 95 men and 1 in 154 women and the mean age at diagnosis is 69 years. What is more, variability between different ethnic groups is observed in terms of gastric cancer incidence, with Hispanics, non-Hispanic Blacks and Asian and Pacific Islanders bearing twice as high rates compared to non-Hispanic Whites and the greatest decline in the incidence rates being observed among Asian and Pacific Islanders. From a geographical perspective Alaska had the greatest incidence rates for gastric malignancy until 2012, while New York took over from 2016-2017. However the number of

states yielding an incidence rate above 8,4 per 100.000 declined from seven in 2001-2002 to only one (New York) by 2016-2017. [33]

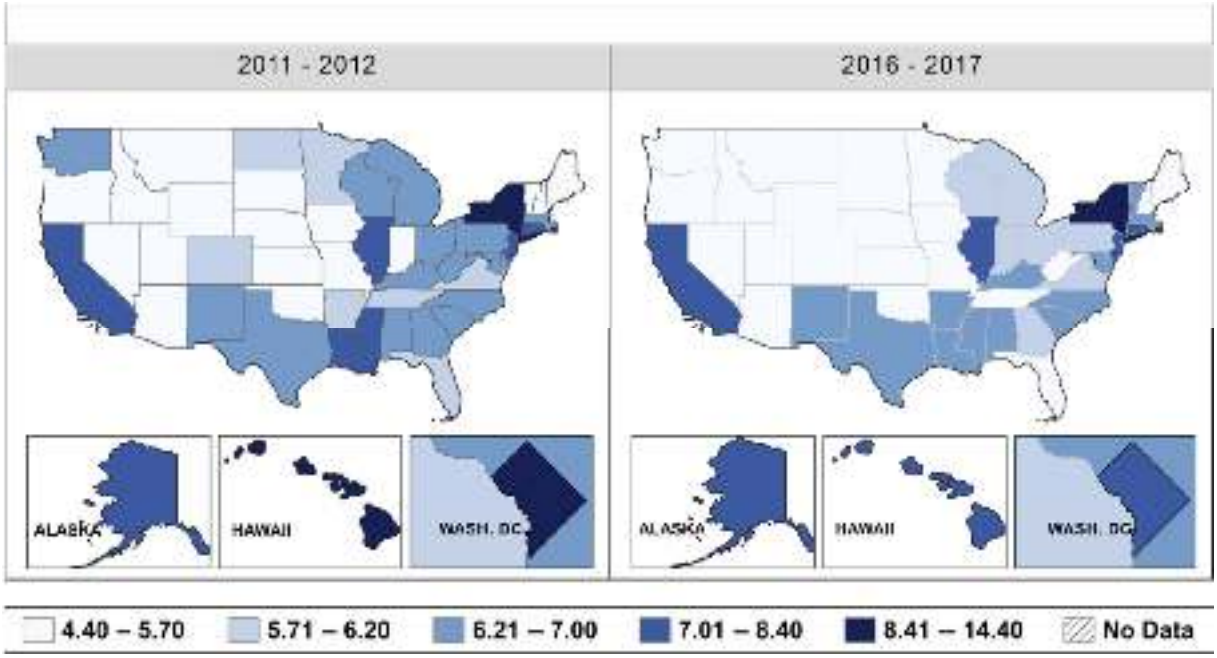

Figure 7: Heat maps showing age-adjusted incidence rates of gastric cancer in the different states of the US, 2012- 2017.

Source: www.cdc.gov/cancer/uscs/public-use

Owing to a large population base, China holds the first place in the amount of patients suffering from gastric malignancy globally being fourth in the global ranking of countries with the highest incidence of gastric cancer (20,6 per 100.000). The decreasing trend during the recent decades has been established in China as much as in other countries, since the age-standardized incidence rate of gastric cancer has dropped from 50,77 per 100.000 to 37,42 per 100.000 from 1990 to 2019. [34] Certain Asian countries however seem to elude this downward trend for gastric cancer, especially high-incidence ones like Korea where gastric cancer rates demonstrate a stable pattern over the years, reaching 60 per 100.000 new cases annually regarding male individuals.

The decreasing pattern has been observed in 29 countries globally between 1980 and 2018, with the incidence for gastric malignancy falling from a range of 2,6 to 59,1 per 100.000 to a range of 2,5 to 56,8 per 100.000. Despite the generally acknowledged decreasing trend of

gastric cancer affecting people aged above 40 years, an increasing trend has been observed among younger individuals, less than 40 years old, in countries like Sweden and Ecuador. [31] In the US the incidence of non-cardia gastric malignancy increased by 1,3% per year among non-Hispanic Whites aged between 25 and 39 years old, especially regarding localized-stage gastric cancer which augmented even further, by 5,28% per year, probably on grounds of overdiagnosis. When it came to Hispanics an analogous increase was noted among these aged less than 50 years, yet it concerned distant-staged gastric cancer, indicating the fact that incidence changes affect Hispanic ethnicity more profoundly. [35] Incidence increases for gastric cancer have also been reported in individuals aged less than 50 from countries like the UK, Chile and Belarus and this can be attributed to modern lifestyle that promotes unhealthy diet and obesity leading to a dysbiotic pattern of the gastric microbiome. Although a threshold for rare cancer denomination could be achieved in some countries in the future, others (especially high-incidence countries) show a stability in their rates partially because of nationwide screening programmes (Japan, Korea) and partially because of a high absolute burden of the disease and constant population expansion and ageing. [36]

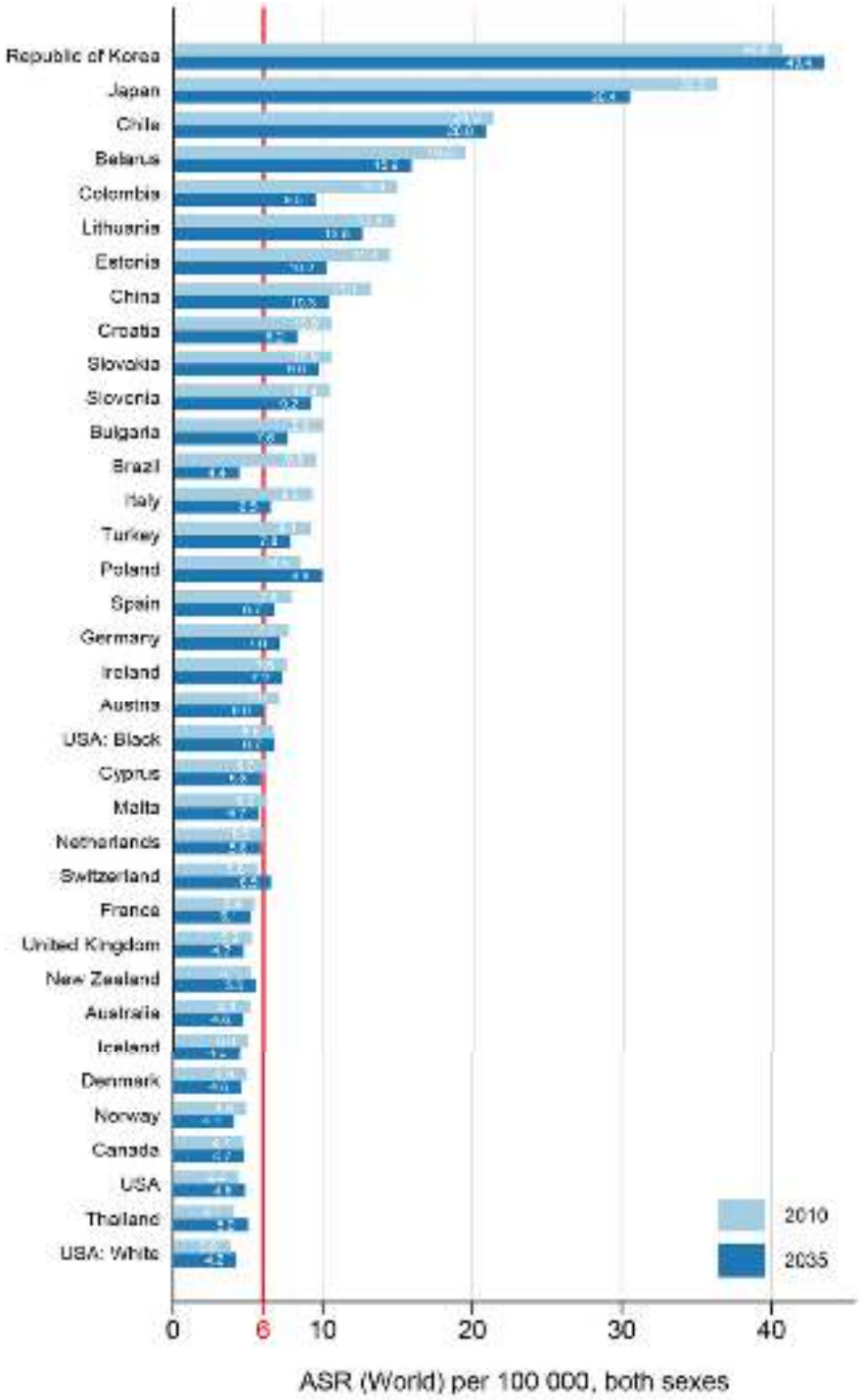

Figure 8: Incidence rates for gastric cancer in 2010 and predicted rates for 2035, for both sexes

A.5 Prognosis and Mortality- Survival rates

The past 2 decades have constituted a turning point in the epidemiology and mortality of gastric malignancy, altering its dynamics as the leading cause of deaths deriving from cancer globally, and putting it to the third place of the most fatal cancers worldwide in 2018, accounting for 783.000 deaths annually (8,3% of all cancer deaths). [12] The cumulative risk for death attributed to gastric cancer for ages 0 to 74 has been estimated at 1,36% for males and 0,57% for females. Countries with high HDI exhibit the highest cumulative risks for gastric cancer (1,61%) compared to low HDI countries that bare the lowest respective cumulative risks (0,49%). Central and Eastern Asia exhibit high mortality rates (15,9 per 100.000), followed by Central and Eastern Europe and Latin America, while the lowest mortality is observed in Northern America (1,8 per 100.000), following mostly the pattern of incidence. Asians' 5-year survival rate surpasses that of Caucasians by 12%. More specifically, gastric cancer is the top-ranking cause of death that is attributed to cancer in 10 countries for males, most of them belonging to the Central and Eastern Asian area, like Iran and Kyrgystan. [18] Survival rates vary according to the stage of the disease at the point of diagnosis, with 5-year survival rates for stage IA being as high as 94%, while stage IIIC reaches 5 years in terms of survival at a mere 18%. A major improvement has been observed concerning the 5-year survival rates especially in localized or regional cancer, thus reflecting the progress in prevention and early diagnosis with endoscopy. In this regard, median relative survival in the US has increased from 10 to 16 months from 2000 to 2014 respectively. Also, 5-year survival rates have improved from 18,8% to 28% for patients diagnosed with gastric malignancy from 2000 to 2010 respectively. Decreasing mortality rates have been observed in several countries with the greatest decrease seen in Norway, Estonia, Ecuador and Finland. However, overall survival rates remain among the lowest for all malignancies and despite the early diagnosis, 35% of all diagnoses occur still at a late distant-stage where 5-year survival rates are below 5%. [33] Overall, the mean 5-year survival rate for Europe, US and the UK is 26%, 31% and 19% respectively.

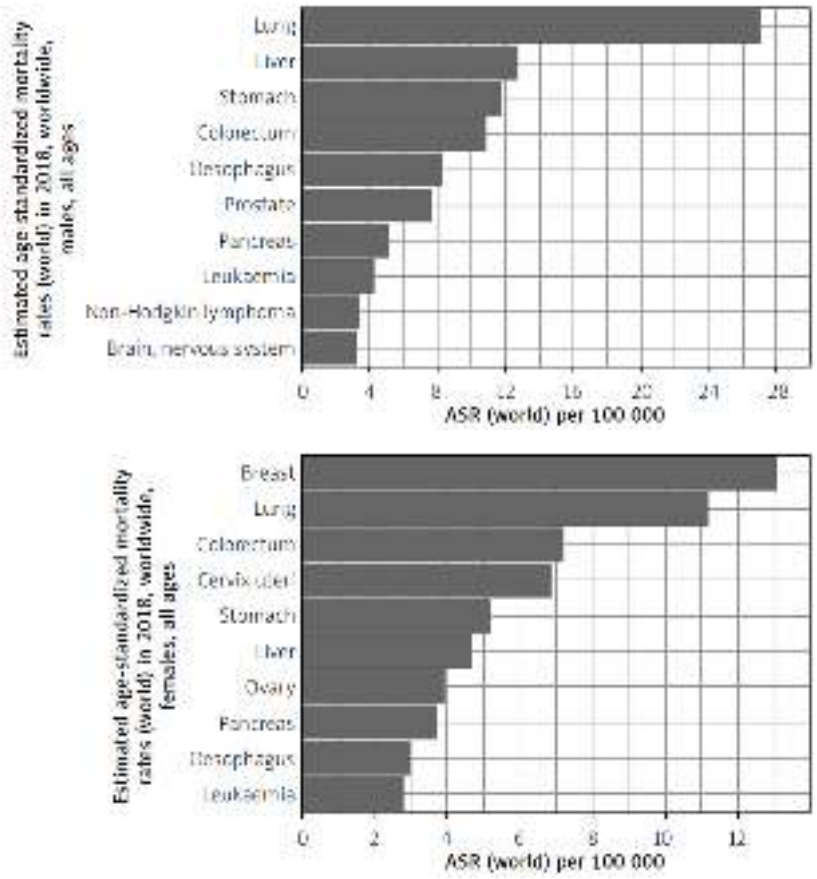

Figure 9: Age-standardized mortality rates in 2018 for males and females, all ages, globally

Source: GLOBOCAN 2018 (http://gco.iarc.fr/today)

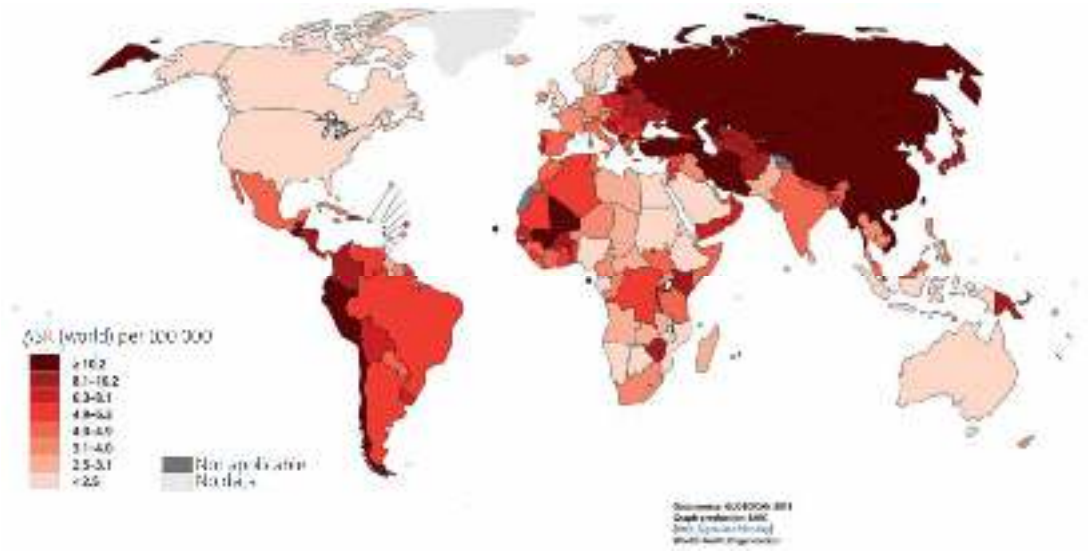

Figure 10: Estimated age-standardized mortality rates for stomach cancer in 2018 for males and females, all ages, globally

Source: GLOBOCAN 2018 (http://gco.iarc.fr/today)

A.6 Prevention

Studies have achieved to demonstrate a significant decrease relating the risk for development of gastric cancer, by 34% after appropriate eradication therapy for H. Pylori. Thus, screening for H. Pylori can be justifiable in populations where the documented rates for gastric cancer are high, but it can be cost-effective even in these areas with malignancy rates as low as 4,2 per 100.000. [37] Also, in the context of primary prevention, a prophylactic oral H. Pylori vaccine has been designed and applied in a randomized controlled trial in children who have not been previously exposed to the bacterium with promising results and a high efficacy in preventing H. Pylori infection. [38] Concerning the role of diet, the International Agency for Research on Cancer has stated that the reduction of gastric cancer risk is “probable” and “possible” with an increase in the consumption of fruit and vegetables respectively. [39]

B. Chapter 2: Current Therapeutic Options

The successful treatment of the various types of gastric neoplasms, and especially the malignant ones, is a very demanding and complicated process, which has been of particular interest of the global scientific community during the last few decades. According to the National Comprehensive Cancer Network (NCCN) Guidelines (Version 2.2022, Gastric Cancer) [40], at all the stages of the therapeutic approach, multidisciplinary collaboration between a number of medical (and even non-medical specialities) is essential, at least once a week. Those specialities include gastroenterologists, pathologists, radiologists, radiation surgical and medical oncologists. Continuous study and review of the patient's clinical, imaging and pathoanatomical picture is an essential component of those regular meetings, with the main objective being the assessment of the progress of the therapeutic intervention and the possible modifications that may be needed.

An essential component for the design of an effective therapeutic intervention is the correct staging of the disease. The system for staging the various forms of gastric carcinomas which is accepted and used by the American Joint Committee on Cancer (AJCC), is the TNM staging one (Tumour, Node, Metastasis), which has been found to have great influence both on the treatment decisions and on the prognosis of the various types of gastric cancer. On the 8th edition of the AJCC Cancer Staging Manual, the stages of the gastric carcinoma have been divided in three sub-categories [41]:

- *Clinical staging (cTNM),* for newly diagnosed who have not been treated yet,
- *Pathologic staging (pTNM),* for patients in whom the tumour has already been resected, but without any prior therapeutic intervention and,
- *Post neoadjuvant pathologic staging (ypTNM),* for patients who, prior to the surgical intervention, received either chemotherapy alone, or chemotherapy along with radiotherapy.

A further differentiation of the 8th edition of the AJCC Cancer Staging Manual is the clear distinction between the esophagogastric junction's tumours and the gastric cardia's tumours, with those having their epicentre located > 2cm into the proximal stomach categorized and staged as gastric carcinomas, whereas those located ≤ 2cm into the proximal stomach, categorized and staged as oesophageal carcinomas [40]. The superiority of the 8th edition in comparison to the 7th edition, was proved by a large longitudinal study published by Ji et al., (2018) [41], in 1.663 patients with various types of gastric carcinoma treated with surgical

excision; the conclusion of the authors was that the 8th edition system was superior to the 7th edition "in terms of discriminatory ability, homogeneity and monotonicity of gradients" in the specific population of Chinese gastric carcinoma patients in which the study was conducted.

According to all the above, Figure 11 presents the recent NCCN guidelines for gastric cancer (Version 2.2022), according to the patient's clinical stage (cTNM staging). It is obvious that in the process of evaluating the patient, before any decision is made for therapeutic intervention, is the assessment of his nutritional status, his family history, strong advice for smoking cessation and detailed evaluation of the medications he / her uses and the possible co-morbidities.

In Figure 12, the basic principles of the systematic treatment of the various forms of gastric cancer are presented in detail, according to the recent guidelines of the NCCN for gastric cancer [40]. Always, the treating physicians should be aware that the regimens for systemic therapy chosen should combine their efficacy with their toxicity profile and the patients' comorbidities.

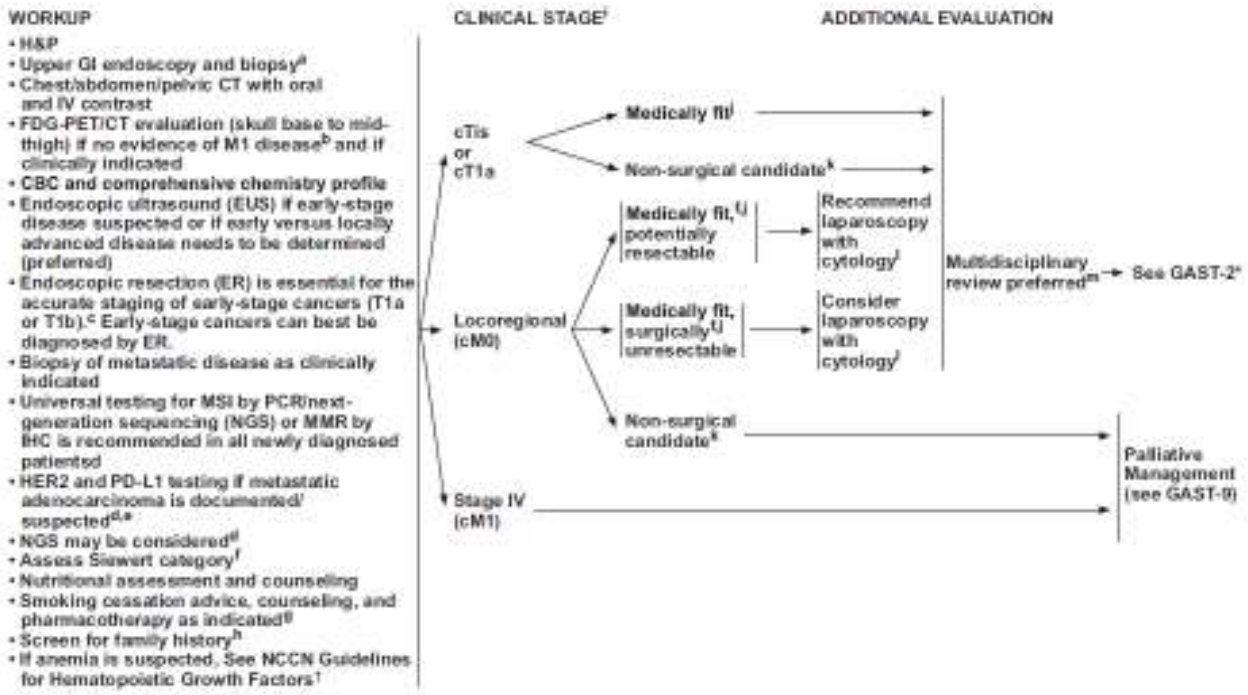

Figure 11: The recent NCCN guidelines for gastric carcinomas (Version 2.2022), according to the patient's clinical stage (cTNM staging).

Source: Ajani et al., (2022) [40].

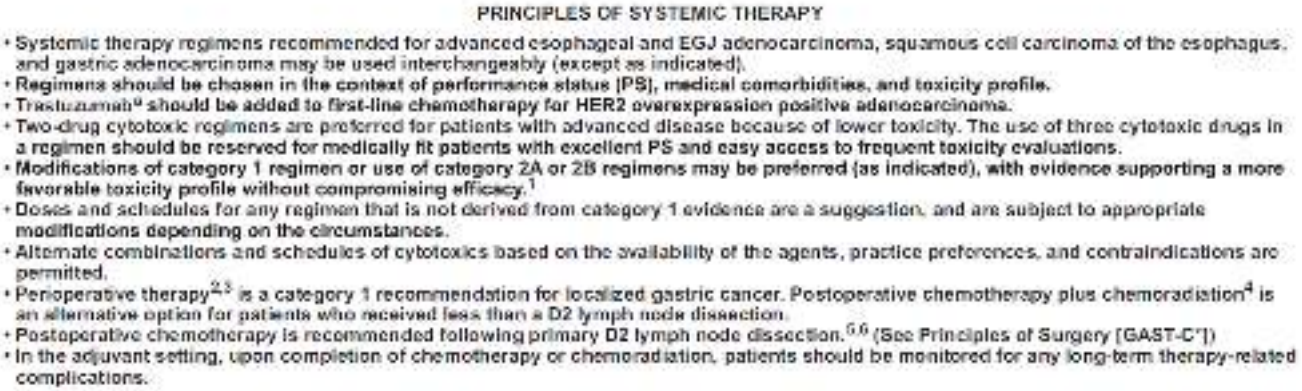

Figure 12: The basic principles of systemic therapy for gastric carcinomas according to the recent guidelines of the NCCN for gastric cancer

Source: Ajani et al., (2022) [40].

The following sections will present the data of the recent literature regarding the various current therapeutic methods for the treatment of the different types of gastric carcinoma, with particular emphasis on the most recently published longitudinal studies along with the systematic literature reviews and / or meta-analyses. The results of those studies are summarized on Table 1

B.1 Localized disease

Today there is an on-growing evidence that localized non-metastatic gastroesophageal and gastric adenocarcinomas are best treated with combined modality therapy, including [42]:

1) Preoperative chemotherapy with or without chemoradiation,
2) Surgical excision of the tumour with adequate lymph node dissection and finally,
3) Postoperative chemotherapy combined with chemoradiation,

Ikoma et al., (2018) [43] published the results of a large longitudinal study involving 16,945 patients with localized clinical T2-4bN0-1M0 gastric adenocarcinoma who were treated surgically in the time period 2006 – 2014 (analysis of the United States National Cancer Dat Base for the years 2006 -2014); the study concluded that:

- A remarkable increase was observed of the use of neoadjuvant (preoperative) chemotherapy during the study's period (34% of the patients in 2006 up to 65% of the patients in 2014).
- Preoperative chemotherapy was used mainly for gastric cardia adenocarcinomas (83% in 2014), in comparison to non-cardia gastric carcinomas (44% of the cases in 2014).
- A statistical significant racial / ethnic disparity was observed for the use of preoperative chemotherapy, in favour of the non-Hispanic white race.

B.1.1 Preoperative chemotherapy

Over the last few decades, the understanding of the various forms of gastric cancer has evolved a lot, and the differences in this have led to significant modifications in the treatment strategy both for the early and for the locally advanced gastric cancer; preoperative (neoadjuvant) chemotherapy is one of the basic therapeutic interventions that have been applied and studied

during the recent years. One of the first published and most well-designed clinical studies regarding the efficacy of preoperative chemotherapy (neo-adjuvant chemotherapy) for the treatment of the resectable adenocarcinoma of the stomach, the esophagogastric junction, and the lower oesophagus was the MAGIC trial [44]; the chemotherapy regimen consisted of three pre-operative and three post-operative chemotherapy cycles, in which patients were administered the following chemotherapeutic agents

1) Epirubicin, intravenously (50 mg/m^2 of body surface area), on the first day
2) Cisplatin, intravenously (60 mg/m^2) on the first day and finally,
3) Fluorouracil, continuous intravenous infusion (200 mg/m^2/day) for 21 consecutive days.

In total 503 patients were randomized, in either the combination therapy group (preoperative chemotherapy followed by surgery - treatment group) or the surgery as a monotherapy group (control group); the medial follow-up period was four years and the patients' overall survival rates was the main end point of the trial. The main results of the study showed that:

- Both groups of patients had the same rates of complications,
- The patients who received combination therapy, in comparison to the patients of the surgery-only therapy, had statistical significant higher rates of overall survival: Death hazard ratio: 0.75, (95% CI 0.60 – 0.93).
- The 5-years survival rate of the patients of the treatment group was 36% versus 23% of the control group patients ($p = 0.009$) and finally,
- The progression-free survival of the patients in the treatment group had hazard ratio 0.66 (95% CI 0.53 – 0.81), $p< 0.001$.

The authors' final conclusion was that the preoperative chemotherapeutic regimen ECF (epirubicin, cisplatin, fluorouracil), is definitely beneficial for the patients with resectable gastric adenocarcinoma, since it improves both the patients' overall survival and their progression-free period. Figure 13 presents the main results of the study.

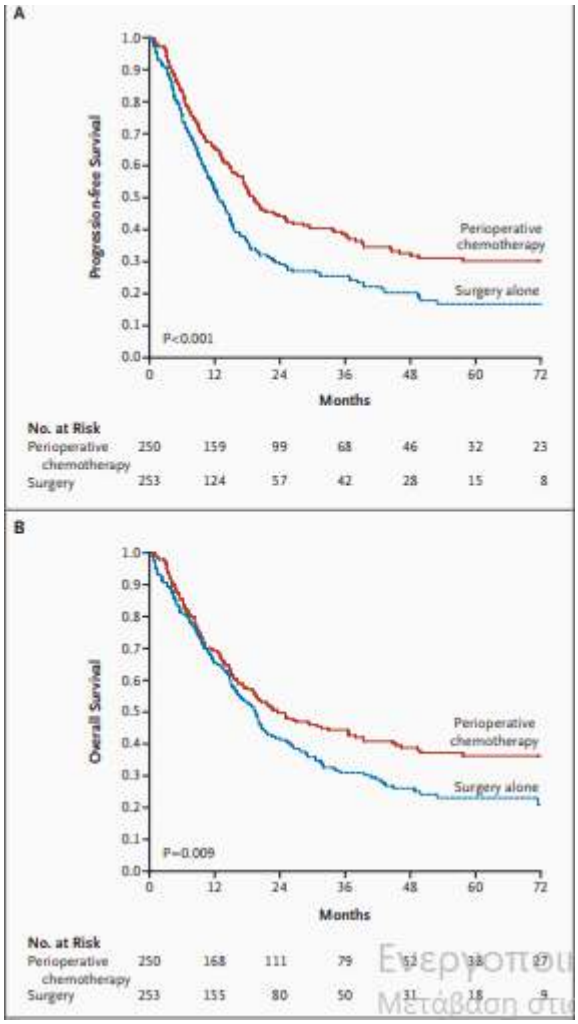

Figure 13: (A): progression-free survival (B) Overall survival (B)

Source: Cunningham et al., (2006).

After thirteen years Al-Batran et al., (2019) [45] published a phase II / III randomized-controlled study in order to evaluate the efficacy of the FLOT chemotherapeutic regimen (fluorouracil plus leucovorin, oxaliplatin and docetaxel) for the preoperative treatment of patients having locally advanced but operable gastric tumours (cT2 or higher, nodal positive cN+ or both), having no clear evidence of distal metastases. 716 in total patients were randomized in two groups: The control group (ECF/ECX group) received three cycles of preoperative and three cycles of post-operative chemotherapy consisting of:

1) Epirubicin, intravenously (50 mg/m^2), on the first day,
2) Cisplatin, intravenously (60 mg/m^2) on the first day and finally,
3) Fluorouracil, continuous intravenous infusion (200 mg/m^2 / day) for 21 days or capecitabine 1250 mg/m^2 orally for 21 consecutive days,

Whereas the treatment group (FLOT group), received four preoperative and four postoperative 2-week circles of chemotherapy consisting of:

1) Docetaxel, 50 mg/m^2,
2) Oxaliplatin, 85 mg/m^2,
3) Leucovorin, 200 mg/m^2 and finally,
4) Fluorouracil, 2600 mg/m^2 intravenously, on the first treatment day.

The primary study's outcome measure was the patients' overall survival (OS). The main results showed were the following:

- In the FLOT group, the patients' median OS was 50 months, whereas in the ECF/ECX group was 35 months.
- The serious side effects of both chemotherapeutic regimens along with the number of toxic deaths were similar in both groups.

The final conclusion of the authors (Al-Batran et al., 2019) [45], was that in locally advanced but resectable carcinomas of the stomach and of the gastro-oesophageal junction, the preoperative FLOT regimen has superior efficacy compared with the preoperative ECF/ECX chemotherapeutic regimen. In Figure 14 the main results of the study are presented.

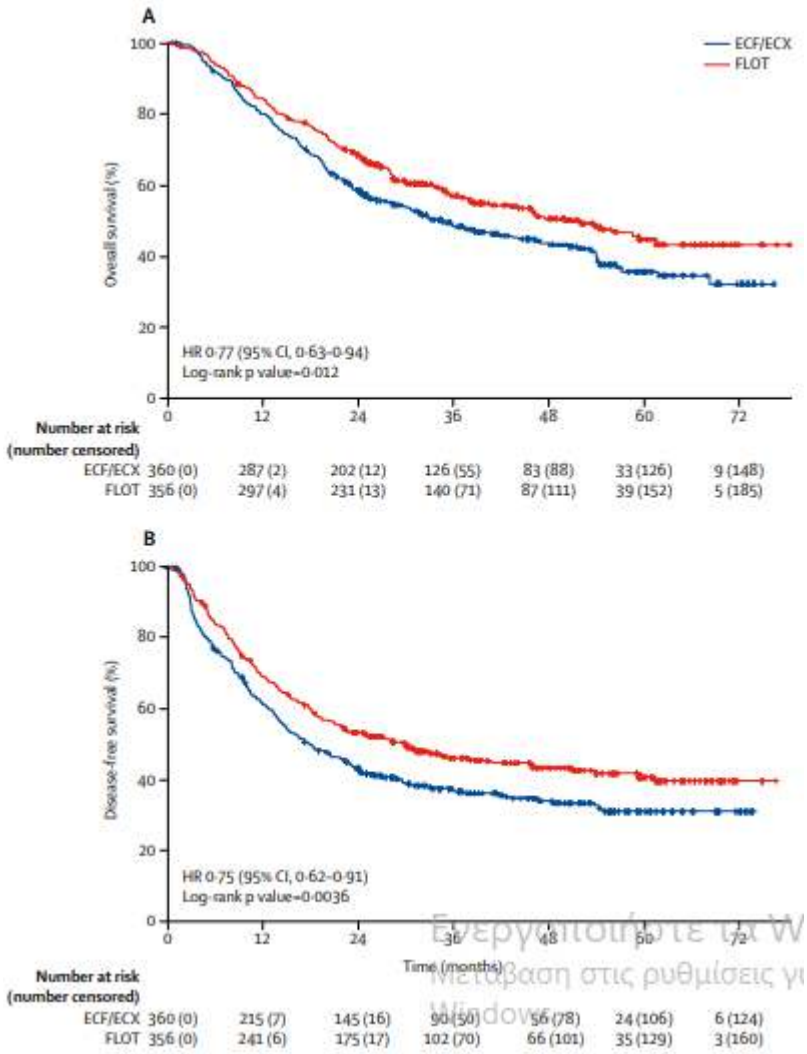

Figure 14: (A): Overall survival (B) Disease free survival rates between the FLOT and the ECF/ECX treatment groups

Source: Al-Batran et al., (2019) [45],

B.1.2 Preoperative (neoadjuvant) chemoradiotherapy

Preoperative chemo-radiotherapy is still regarding as a category 2B (based on lower level evidence) treatment for patients with various types of gastric carcinoma [42]. Ajani et al., (2006) [46], in published the results of a phase II multicentre cohort trial, including 43 patients with localized gastric adenocarcinoma (stages IB, II and III). The treating regimen was:

1) Two circles of fluorouracil, leucovorin and cisplatin (induction to the therapy),
2) Combination of radiotherapy plus chemotherapy (fluorouracil and paclitaxel) and,

3) Surgical resection of the tumour, 5 – 6 weeks after the chemo-radiotherapy treatment was completed.

The trial's main results showed that the preoperative (neoadjuvant) combination of chemotherapy and radiotherapy achieved, in patients with localized gastric carcinomas, complete pathologic response in more than 20% of the participants; moreover, the was a significant improvement of the quality of the subsequent surgical intervention. According to the authors (Ajani et al., 2006) [46], the combination, neo-adjuvant chemo-radiation regimen can be beneficial in this group of patients.

B.1.3 Adjuvant (postoperative) chemotherapy

Data from the recent literature show that for those patients who have already undergone surgery in order to remove a gastric tumour, for which the histologic examination showed T3 or T4 lesions, or node (+) disease, postoperative (adjuvant) chemotherapy is recommended [42]. One of the most important clinical studies demonstrating the above was published by Bang et al., in 2012 [47]; it was the CLASSIC, phase III open label randomized-controlled trial, which evaluated the efficacy of the postoperative chemotherapeutic combination regimen of capecitabine plus oxaliplatin immediately after a D2 gastrectomy in patients with resectable gastric adenocarcinomas.

The study took place in 37 centres of China, South Korea and Taiwan, with in total 1.035 participants; the patients in the control group had surgery alone (D2 gastrectomy), whereas the patients in the intervention group, after the surgical intervention received:

1) Capecitabine, per os, (1.000 mg/m^2) two times per day, during the 1st-14th day, for eight cycles (each cycle lasting for three weeks) and,
2) Oxaliplatin, intravenously, (130 mg/m^2), on the first day of every therapeutic cycle.

The main outcome measure of the trial was the patients' 3 year disease-free survival rates. The trial's main findings (mean follow-up 34.3 months) showed that:

- The intervention group had statistical significant improvement of the 3 year disease-free survival rates, in comparison to the control group: 74% vs 59% , $p < 0.0001$, HR 0.56 (95% CI 0.44-0.72)

- Serious complications or side-effects because of the treatment (grade 3 and grade 4) occurred in the 56% of the patients of the intervention group and in only 6% of the patients in the control group; the commonest adverse events were nausea, neutropenia and loss of appetite.

The final conclusion of the authors (Bang et al., 2012) [47] was that this specific adjuvant chemotherapeutic regimen after a D2 - type gastrectomy in patients with resectable gastric adenocarcinoma should definitely be considered as a treatment option. Figure 15 presents the patient's 3 years disease free survival rates.

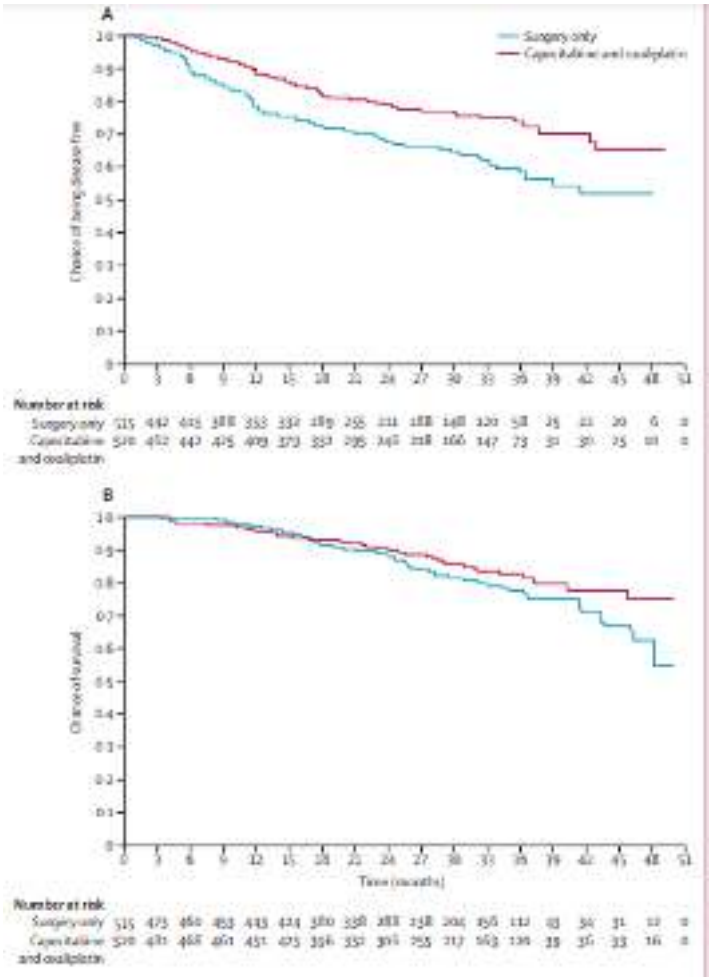

Figure 15: Three - year disease-free survival (Panel A) and OS (Panel B) rates

Source: Bang et al., 2012) [47]

Just recently, Zhang et al., (2021) [48], published the findings of the RESOLVE trial. This was an open labelled, phase 3 randomized-controlled study, in which the researchers studied the efficacy of the combination of preoperative or postoperative oxaliplatin plus S-1, versus postoperative oxaliplatin plus capecitabine, for the treatment of a population of 1.022 patients suffering from locally advanced gastric adenocarcinoma and who were treated with D2 - type gastrectomy. The participants of the study were randomized into three groups.

1) Adjuvant CapOx group (capecitabine plus oxaliplatin),
2) Adjuvant SOX group (oxaliplatin plus S-1) and,
3) Neoadjuvant (preoperative) SOX group.

The main end-point of the study was the patients' 3-year disease-free survival rates of both the study groups. The main results of the study showed that 1) the neoadjuvant SOX group had a clinically meaningful improvement in comparison to the adjuvant CapOx group and 2) the adjuvant SOX group was not inferior to the adjuvant CapOx group. Figure 16 summarizes the above mentioned results.

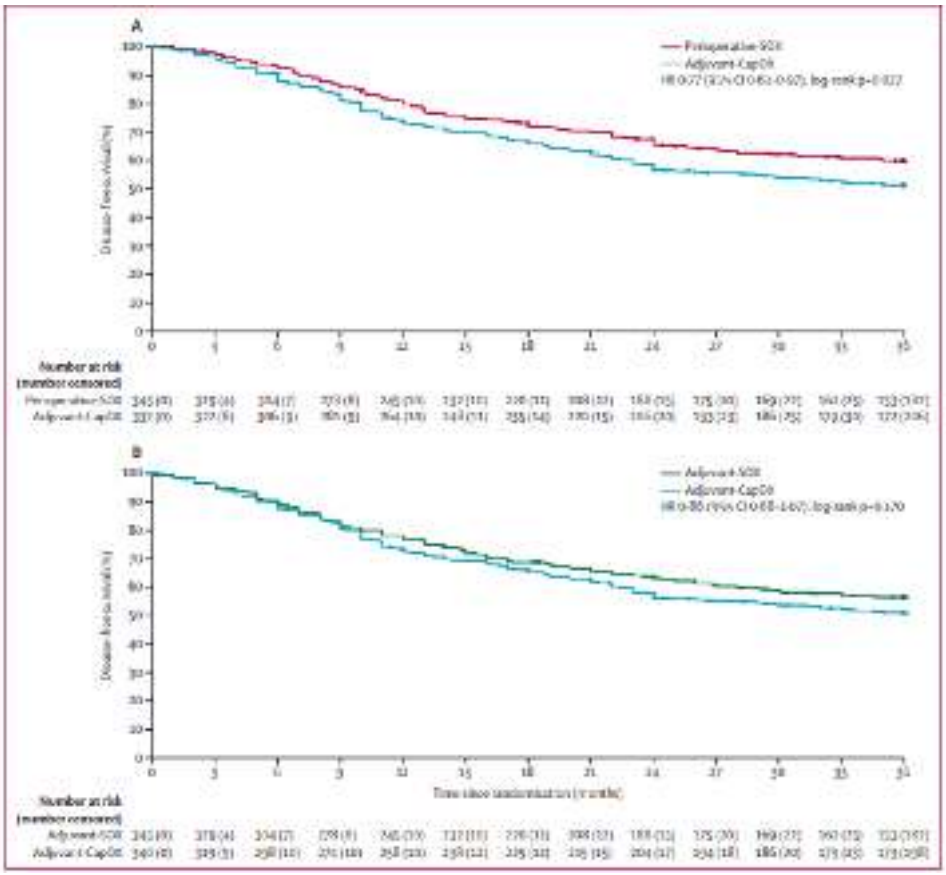

Figure 16: Three - year disease-free survival of preoperative SOX regimen (Panel A), versus postoperative CapOx regimen (Panel B)

Source: Zhang et al., (2021) [48].

B.1.4 Adjuvant (postoperative) chemoradiotherapy

Despite the fact that, as has already been shown, the effectiveness of postoperative (adjuvant) chemotherapy in localized gastric tumours is no longer questioned, the role of the postoperative radiotherapy is less certain and still under research. Just recently, Park et al., (2021) [49], published the results of the ARTIST 2 trial, a randomized-controlled study, involving 546 participants, suffering from stage II or III, node positive, gastric adenocarcinoma, who have got treatment with D2 surgical excision of their tumour. In this trial, the researchers compared the effectiveness in the treatment of stomach tumors of this category of three different treatment protocols:

1) S-1, per os, 40-60 mg, two times per day, four weeks on / two weeks off for one year,
2) S-1 , per os, 40-60 mg, two times per day, two weeks on / one week off, plus oxaliplatin 130 mg/m^2 every three weeks for a total period of six months (the SOX group) and finally,
3) SOX regimen plus 45Gy radiotherapy (the SOXRT group).

Once again, in this trial, primary end point was the 3-years free-of disease survival of the patients. After a 47 months median follow-up period, the authors concluded that 1) Both the SOX and the SOXRT regimen were superior to the S-1 regimen in prolonging statistically significant the patients' 3-years disease-free survival rates (64.8%, 74.3% and 72.8% respectively for the S-1, SOX and SOXRT groups), whereas, 2) There was no statistically significant difference between the SOX and the SOXRT group. All the adverse effects recorded were the anticipated ones for each treating regimen, and were well-tolerated by the patients. The final conclusion of the authors (Park et al., 2021) [49], was that adding adjuvant radiotherapy to the SOX regimen did not had additional benefit in patients suffering from operable stage II or stage III, node (+) gastric adenocarcinoma. The above mentioned findings are shown in figure 17.

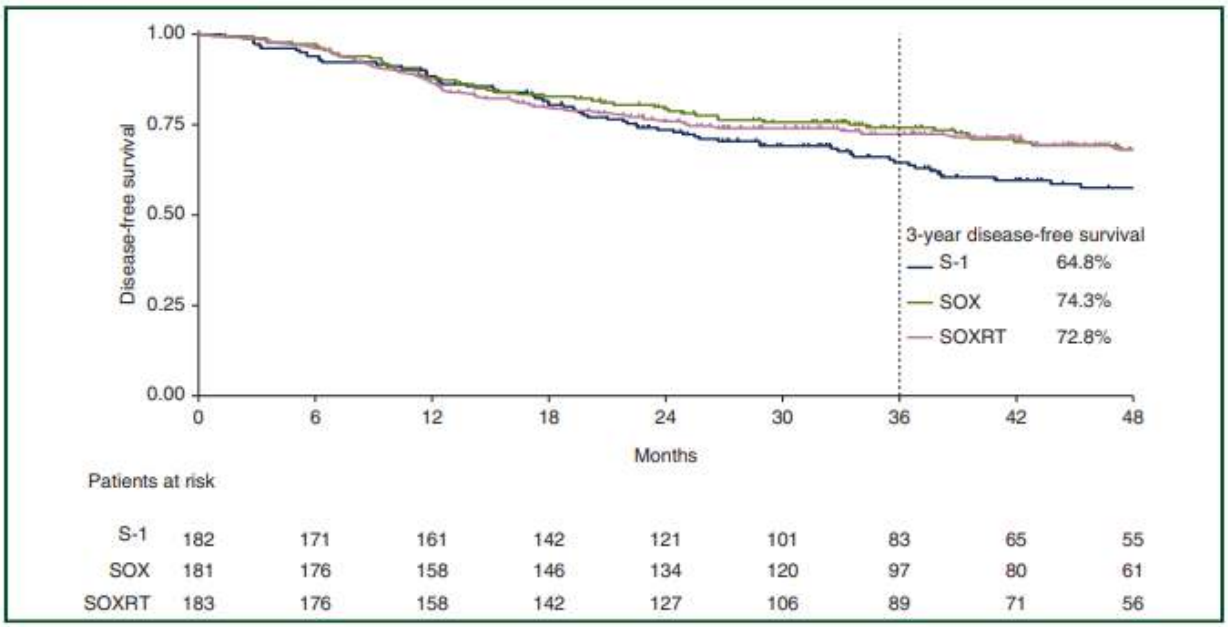

Figure 17: Three - year disease-free survival in the three arms of the ARTIST II clinical trial

Source: Park et al., (2021) [49]

B.1.5 Surgical excision of the gastric tumor

Total gastrectomy and subtotal gastrectomy are the two main surgical options for the treatment of operable gastric carcinomas. According to Joshi and Badgwell., (2021) [42], the treating surgeons should be particularly careful and meticulous in those cases in which they decide to proceed to a type of partial gastrectomy (such as a limited proximal gastrectomy or a wedge-type, non-anatomic gastrectomy), for various reasons, including the following:

1) A large proportion of gastric adenocarcinomas, which reaches even 75%, especially in the populations of western countries are poorly differentiated, which necessitates the performance of wide surgical resection in order to ensure the negative surgical margins [50],
2) The rates of positive lymph nodes are significant: 10% for T1a tumors, 34% for T1b tumors and 44% for T2 tumors [51],

3) Proximal gastrectomy, with dissection of the various branches of the vagal nerve significantly increases the rates of the particularly troublesome postoperative complication of chronic gastroesophageal reflux disease and lastly,
4) Most of the authors agree that in order to achieve an adequate D2 lymph node dissection, an anatomical gastric resection is needed [42].

The steps of an anatomical D2 subtotal gastrectomy, along with the subsequent surgical reconstruction include [42], Figure 18:

1) Separation of the greater momentum form the traverse mesocolon,
2) Transection of the duodenum, the right gastric and the right gastroepiploic vessels,
3) Dissection of the left gastric vessels and finally
4) Gastric transaction.
5) In those cases in which the tumor is more proximally, the short gastric vessels are transected as well.

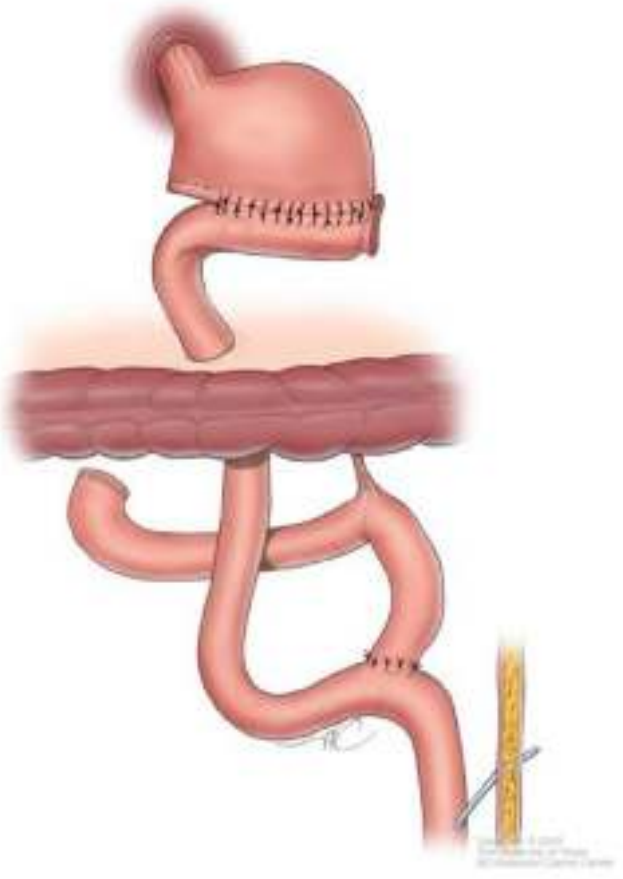

Figure 18: Gastric reconstruction after a subtotal gastrectomy

Source: Joshi and Badgwell., (2021) [42]

B.1.6 Endoscopic resection of the gastric tumour

During the recent years, endoscopic submucosal resection of the tumour has been considered as an effective method of treating gastric neoplasms, especially those which are on the early stages of their development; it is a surgical technique, which, despite the fact that it is quite demanding in its execution, is able to achieve excellent *en bloc* excision of the existing superficial gastric tumours, having very good therapeutic results and of course avoiding the classic open surgical interventions. This method has begun to be applied is Asian countries with very good therapeutic results and at the present time is considered as the basic therapeutic option for the treatment of early stages gastric tumours in these regions of the world [52, 53].

In recent years, endoscopic submucosal resection of gastric tumours has been applied with increasing frequency in Western countries as well, with the result being the relevant literature of the efficacy of the method increasing significantly. Just recently, Benitez-Goni et al., (2023) [54], published the results of a systematic literature review and meta-analysis regarding the efficacy of the endoscopic submucosal excision for the treatment of superficial gastric tumours in non-Asian countries. The authors analysed and presented the findings of 27 relevant clinical studies (2 coming from North America, 11 from South America and 14 from Europe), involving 1.875 in total gastric tumours. The main results of the systematic review were the following:

- The rate of *en bloc* resection was 96% (95% confidence internal: 94% - 98%), the rate of R0 resection was 85% (95% confidence internal: 81% - 89%), and the rate of curative resection was 7% (95% confidence internal: 73% - 81%).
- Taking into account only the tumours which were histologically identified as adenocarcinomas, the overall curative resection rate was 75% (95% confidence internal: 70% - 80%).
- There were only a few serious complications from the application of this technique, with the most commonly reported ones being bleeding (5%) and perforation (2% of all the cases).

The final conclusion of the authors (Benitez-Goni et al., 2023), [54] were that endoscopic submucosal tumour dissection can definitely be the first choice therapy for superficial gastric neoplasms; the increasing frequency of application of the method in the Western countries is expected in the near future to have similar therapeutic results to those recorded in the Asian countries.

B.1.7 Conclusions

Having the main objective to summarize the results of the recent literature, Kumar et al., (2022) [55] (from the American Radium Society – ARS) published the results of a systematic literature review in order to provide specific guidelines regarding the treatment of locoregional gastric adenocarcinoma. After extensively analysing a number a phase 2, 2R and 3 clinical trials published between 2010 and 2020, the authors reached to the following conclusions:

1) Patients with medically operatable – locally advanced gastric cancer:
   - Preoperative chemotherapy is the strongest recommendation.
   - Acceptable alternative could be surgical excision plus adjuvant chemotherapy or chemo-radiotherapy.
2) Patients who have already undergone surgical excision of stage I – III gastric cancer: Post-operative (adjuvant) chemotherapy or post-operative chemo-radiotherapy.
3) Patients with locally advanced disease who received pre-operative (neo-adjuvant) chemotherapy, but no regression of the tumour was noted: Post-operative (adjuvant) chemotherapy or post-operative chemo-radiotherapy.
4) Patients with non-operable gastric tumours due to medical reasons: Concurrent chemo-radiotherapy.

The final conclusion of the authors, (Kumar et al., 2022, American Radium Society – ARS) [55] was that pre-operative (neo-adjuvant) or post-operative (adjuvant) chemo-radiotherapy improves the survival rates of patients with gastric carcinomas in comparison to surgery alone; either in non-operatable tumours, chemoradiotherapy should be regarded as the best treatment option.

Table 1: The results of the analysed clinical studies

Author, Country	Type of Study	Participants / Intervention	Outcome measures / Results	Main Conclusions

Ikoma et al., (2018) [43], U.S.A.	Longitudinal study (USA National Cancer Data Base), years 2006 – 2014	16.945 patients with localized clinical T2-4bN0-1M0 gastric adenocarcinoma	Treatment regimens. Preoperative chemotherapy increased from 34% in 2006 to 65% in 2014. More commonly used for cardia (83%) than non-cardia tumors (44%)	Remarkable increase of the use of preoperative chemotherapy over the years, mainly for gastric cardia adenocarcinomas. There is a racial disparity for use of preoperative chemotherapy, in favour of the non-Hispanic with race
Cunningham et al., (2006) [44] , U.S.A. The MAGIC trial	Randomized – controlled study	503 patients with operable gastric adenocarcinoma Preoperative chemotherapy regimen ECF vs surgery alone	Survival rates (overall, and free of the disease). ECF group: HR for death: 0.75, p=0.009. 5-year survival rate: 36% vs 23%. HR for progression: 0.66, p<0.001.	The preoperative ECF regimen in beneficial, since it improves both the progression-free period and the patients' overall survival rates
Al-Batran et al., (2019) [45] , Germany. The $FLOT_4$ trial	Phase 2/3 randomized-controlled study (RCT)	716 patients with locally advanced but operable gastric tumours. FLOT regimen versus ECF/ECX regimen	Survival rates (overall, and free of the disease). OS: 50 months vs 35 months. HR: 0.77. Similar results for serious side effects (27% vs 27%), for toxic deaths (2 for each group) and for hospitalization for toxicity (25% vs 26%).	Preoperative FLOT chemotherapeutic regimen is superior to the ECF/ECX one for the treatment of patients with locally advanced, but operable gastric carcinomas
Ajani et al., (2006) [46], U.S.A.	Phase 2 cohort, multicentre trial	43 patients with local adenocarcinoma. Efficacy of preoperative (neoadjuvant) chemo-radiation : FLC, followed by radiation + FP	Rates of pathologic complete response, survival and safety. pathCR rate: 26%, R0 rate: 77%. At 1 year, 82% patients living with pathCR, vs 69% with less than pathCR. Grade 4 toxicity in 21% of the patients.D2 dissection in 50% of the patients.	>20% complete pathologic response rate; significant improvement of the surgical interventions' quality
Bang et al., (2012), [47], South Korea. The CLASSIC trial	Phase 3, open-labelled, RCT	1.035 patients with resectable gastric tumour, who were treated with D2 gastrectomy. Efficacy of adjuvant chemotherapy with capecitabine plus oxaliplatin + surgery vs surgery alone	Three – years survival rates, free of the disease. 3-years free of disease rate 74% vs 59% (HR 0.56, p< 0.0001). Grade 3/4 adverse effects (56% vs 6%)	Patients in the adjuvant chemotherapy group had statistical significant improvement of the 3-years disease-free survival rates in comparison to the control group (74% vs 59%).
Zhang et al., (2021) [48], China. The RESOLVE trial	Phase 3, open-labelled, RCT	1.022 patients with locally advanced adenocarcinoma Efficacy of adjuvant SOX or	Three – years survival rates, free of the disease 51.1% vs 56.5% vs 59.4%. HR: 0.77(p=0.028) and 0.86 (p=0.17)	The neoadjuvant SOX group had a clinically meaningful improvement compared to the adjuvant CapOx group; the adjuvant

		CapOx regimen versus neoadjuvant SOX	Serious side effect similar in all groups. No treatment-related deaths	SOX group was not inferior to the adjuvant CapOx group.
Park et al., (2021) [49], South Korea. The ARTIST II trial	Phase 3, open-labelled, RCT	546 patients with stage II / III, node (+), resectable adenocarcinoma. Comparison S-1, SOX and SOXRT regimens	DFS at 3 years. DFS rates: 64.8% vs 74.3% vs 72.8%. S-1 vs SOX: HR= 0.692 (p= 0.042), S-1 vs SOXRT: HR= 0.724 (p= 0.074). SOX vs SOXRT: HR= 0.971, (p= 0.879)	The addition of postoperative radiation to the SOX chemotherapeutic regimen does not improve the 3-years disease-free survival rates of this group of gastric cancer patients
Benites-Goni et al., (2023) [54], Peru	Systematic literature review and meta-analysis (27 clinical trials)	1.875 superficial gastric lesions treated with endoscopic submucosal gastric dissection	Rates of 1) curative, 2) R0 and 3) en block resection,; complications of the method. 96% *en bloc* resection, 85% R0 resection, 77% curative resection; Bleeding 5%, perforation 2%	The method can definitely be therapy of first choice in order to treat superficial gastric neoplasms.

B.2 Metastatic or unresectable gastric tumors

The therapeutic management of extensive gastric carcinomas that have already yielded distant metastases and thus are characterized as unresectable is a major challenge for treating

physicians. In all cases the main goal of the therapeutic intervention is palliative, in order to [42]:

1) Control the disease itself, along with its symptoms,
2) To improve, as far as possible, the quality of life of the patients and their ability to carry out the activities of their daily living with easy and,
3) To extend the patients' life as possible.

A number of chemotherapeutic agents are available for this palliative treatment, including platinum, irinotecan, taxanes and fluoropyrimidines; the choice of the chemotherapeutic drug or the combination of the drugs depends on the overall health status of the patient, in combination to the co-morbidities from which the patient suffers, along with the toxicity characteristics of the chemotherapeutic regimen. In the following paragraphs, some of the most recent relevant systematic literature reviews will be presented in detail (Table 2).

Feng et al., (2020) [56] in a systematic literature review and meta-analysis studied the safety and efficacy of S-1- based chemotherapy in comparison to capecitabine-based regimen for the treatment of recurrent or metastatic gastric cancers. They included six clinical trials (561 patients in total) which were published up to June 2019; the outcome measures of the studies included the objective response rate (ORR), the 1, 2 and 3 years overall survival rate, the 6, 12 and 18 months progression free survival rate (PFSS) and the serious regimens' adverse effects. The main findings of the meta-analysis were the following:

1) There was no statistically significant differences between the two different chemotherapy regimens in ORR, overall survival rate and the PSSR and,
2) The capecitabine-based regimens had statistically significantly significant higher rates of hand-foot syndrome ($p < 0.01$) and grade 3 and 4 neutropenia ($p<0.05$).

The final conclusion of the authors (Feng et al., 2020) [56] was that, although, in terms of efficacy, both regimens produced the same results, S-1 based chemotherapy regimens produced less serious adverse effects, and thus should be the first choice for the treatment of patients suffering from recurrent or metastatic gastric carcinomas, in favour to capecitabine-based chemotherapeutic regimens.

In another systematic review of the literature, Chen et al., (2013) [57] compared the efficacy of the DCF (Docetaxel, Cisplatin and Fluorouracil) chemotherapeutic regimen with nan-taxane-containing regimens in order to treat inoperable, metastatic or recurrent gastric carcinomas.

They included 12 randomized-controlled clinical trials, with 1.089 patients in total; the primary outcome measures were the 1- and 2- years overall survival rates, whereas the secondary ones included the median survival time, the median time to progression of the disease, the response rate of the treatment and the serious adverse effects / toxicities of the chemotherapeutic regimens used. The main conclusion of the authors was that the DCF regimen produced better therapeutic response in comparison to the non-taxane containing regimen (2-year overall survival rate: RR: 2.03, $p = 0.006$); in addition, the adverse effects of the DCF regimen (febrile neutropenia, leukopenia, neutropenia and diarrhea) can be regarded as acceptable.

In one of the most recently published phase III randomized-controlled studies, Rosati et al., (2022) [58], compared the efficacy of fractioned docetaxel, oxaliplatin and capecitabine (low tox) chemotherapeutic regimen, in comparison to epirubicin, oxaliplatin and capecitabine (EOX) regimen (the LEGA trial). 169 participants with unresectable, metastatic or locally advanced adenocarcinoma took place in the study, having main outcome measure the progression free survival, whereas the secondary ones included the overall survival, the disease control rate, the overall response rate and the patients' tolerability of both regimens. The results showed no statistically significant differences between the two regimens in most of the studies' outcome measures, concluding that the novel, (low-tox) triplet regimen, based on the fractional dose of docetaxel does not provide superior results in comparison to the EOX chemotherapeutic regimen. The Kaplan-Meier curve for the main outcome measure of the study (progression-free disease survival) is presented in Figure 19.

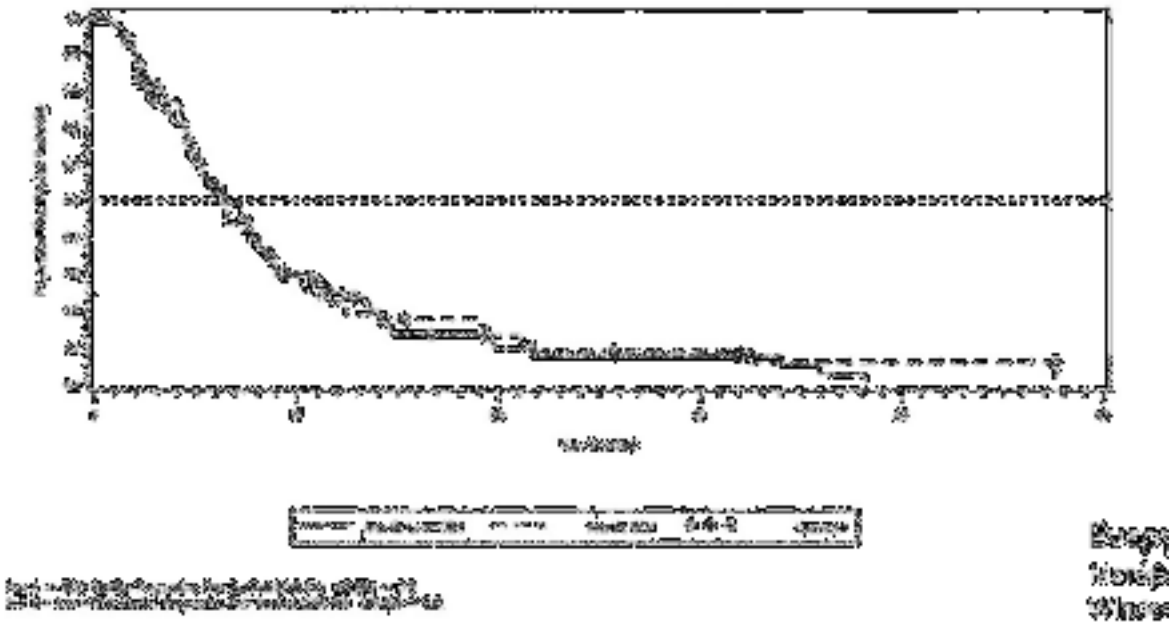

Figure 19: The Kaplan-Meir curve for the progression-free disease survival

Source: Rosati et al., (2022) [58]

The final decision on the type of therapeutic intervention that should be followed in patients with inoperable, metastatic, recurrent or locally advanced gastric cancer - whether a chemotherapy regimen or just palliative / best supportive care treatment should be used, depends on both the overall health condition and the patient's own will. One of the most reliable objective measures for the clinical condition of the patients is the ECOG Performance Status Scale for patients with cancer [59]. In this scale, patients with a score of ≥ 3 are offered only best supportive / palliative care, whereas if the score is ≤ 2 systemic therapy or chemoradiation along with palliative therapy should be considered, if they have not received previously [40]. Figure 20 summarizes the recent NCCN guidelines for gastric cancer for the palliative management of the disease.

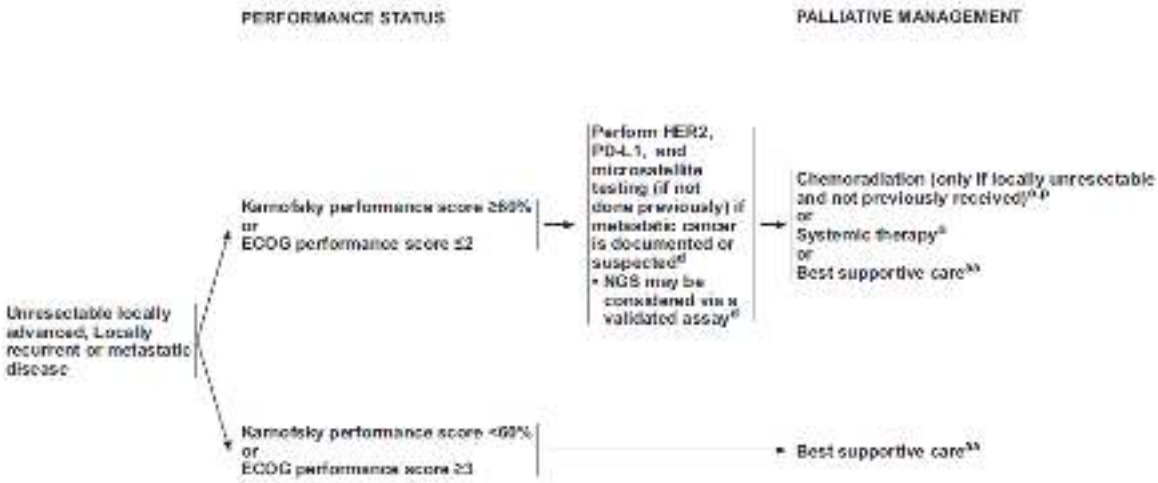

Figure 20: The NCCN guidelines (Version 2.2022) for the palliative management of gastric cancer**.**

Source: Ajani et al., (2022)

In conclusion, and taking into account all the above mentioned research data of the recent literature, the recommended therapeutic approach, especially in patients with good physical condition and local disease, includes surgical resection of the primary lesions with margins >5 cm, D2 (extended) lymph node dissection without pancreatectomy and with splenectomy only when the spleen is involved by the disease. Nowadays, in patients with local-peripheral gastric cancer, international guidelines recommend peri-operative (neo-adjuvant and adjuvant) chemotherapy; this therapeutic regimen includes chemotherapy before and after surgery. This approach improves overall survival. The chemotherapy regimens used are generally well tolerated, with the majority of patients managing to complete both pre- and post-operative chemotherapy without major complications and side-effects.

The international medical community is trying to further improve the results which have been already achieved by further categorizing patients. In the last few years the aim has been to identify sub-groups of patients with particular pathological characteristics where more specific treatment can achieve even better results. In this context, the addition of targeted therapy to chemo-radiotherapy is being explored.

The place of immunotherapy as part of perioperative treatment is also being explored and there is a hope to have a clear answer in the coming years. Small studies that have been done for metastatic disease have shown encouraging results. However, the question remains as to which immuno-histochemical marker should be used to find the group of patients who will benefit from immunotherapy. In all cases, due to the complexity of the disease, all the cases should be discussed in the Oncology Board with the participation of all relevant specialties such as Gastroenterologist, Radiologist, Surgeon, Radiotherapist and Oncologist, pre-operatively, in order to cover all possible possibilities, and to individualize and determine the most appropriate treatment algorithm for each patient.

The following sections of this thesis will present in detail the recent research data, both at the theoretical level and at the level of clinical practice, in relation to the effectiveness and prospects of the various innovative therapies (including immunotherapy) that have gradually started to move from the experimental stage to clinical practice for the treatment of the various forms of gastric cancer.

Table 2: Metastatic or non-resectable gastric tumours

Author, Country	Type of Study	Participants / Intervention	Outcome measures / Results	Main Conclusions
Feng et al., (2020), [56], China	Systematic literature review / meta-analysis (6 clinical trials, phase II)	561 patients with recurrent or metastatic gastric carcinomas. Comparison of S-1 based therapy to capecitabine-based therapy	Objective response rate, PFSR, OSR and adverse effects No statistical significant difference in ORR (6, 12, 18 months, 1 and 2 years). Capecitabine regimens higher incidences of hand-foot syndrome ($p < 0.01$) and grades 3-4 neutropenia ($p = 0.03$).	S-1 based regimens produced lesser serious adverse effects. They should be preferred over capecitabine-based regimens
Chen et al., (2013), [57], China	Systematic literature review / meta-analysis (12 RCTs)	1.089 patients with recurrent or metastatic gastric carcinomas. Comparison of the DCF chemotherapeutic regimen to non-taxane-containing regimens	1- and 2- years OSR, survival time, time to progression of the disease, response rate of the treatment and the serious adverse effects / toxicities Partial response rate: 38.8% vs 27.9%, $p = 0.0003$. Progressive disease rate: 18.9% vs 33.3%, $p = 0.0005$. Comparable chemotherapy related mortality: RR=1.23, p=0.49	The DCF regimen produced better therapeutic response in comparison to the non-taxane containing regimen (2-year overall survival rate: RR: 2.03, $p = 0.006$); in addition, the adverse effects of the DCF regimen (febrile neutropenia, leukopenia, neutropenia and diarrhea) can be regarded as acceptable
Rosati et al., (2022) [58], Italy. The lega trial	Phase 3 randomized-controlled study -	169 patients with unresectable, metastatic or locally advanced gastric carcinomas. Comparison of a novel low-tox regimen (based on the fractional dose of docetaxel – arm 1) versus the EOX regimen (arm 2)	PFS, OSR, overall response rate, disease control rate and tolerability of the treatment. PFS: 6.3 months in arm 1 vs 6.3 months in arm 2. OS: 12.4 months in arm 1 vs 11.5 months in arm 2. ORR: 33% in arm 1 vs 24%. in arm 2. DCR: 68% in arm 1 vs 67%. in arm 2. Treatment modifications and grade ≥ 3CTC higher in arm 2 (78% vs 91%, p=0.017 and 35 vs 42).	No statistically significant difference between the two chemotherapeutic regimens

C. Chapter 3: Novel therapeutic options

During the recent years, a number of novel - innovative therapies have been studied and have begun to be applied in the treatment of gastric neoplasms; these are therapeutic interventions which are primarily based on the latest developments in immunotherapy and anti-angiogenic therapy. In addition, important scientific advances have also been made in the study of new biomarkers that will be useful both for diagnosis and for studying the progression of the disease.

C.1 Immunotherapy for the treatment of gastric cancer

Unlike chemotherapy, immunotherapy is a novel treatment that targets the patients own immune system, stimulating and releasing T-cells, the body's special cells which attack and destroy cancerous tumours. This is a process which causes the internal mechanism which exists in every human being to be mobilized for his/her own benefit [60]. The main drugs used for this novel therapeutic intervention are the "immune checkpoint inhibitors" anti PD-1, anti PDL-1 and anti CTLA-4, which, all of them, act on the patient's T-lymphocytes bound by specific bonds. Those inhibitors release specialized "killer-cells", which are driven into the tumour's microenvironment having their main purpose the destruction of the cancerous cells.

Those drugs belong to the class of monoclonal antibodies and have been used in the clinical practice for the treatment of various neoplastic diseases since 2011; today, they are used either in combination with each other, or in combination with other drugs, such as the "targeted therapy drugs". Targeted therapy is a novel approach in drug and vaccine development, which results in an new clinical practice based on specific genetic information. This novel approach, with the close contribution of molecular biology today is described by the term of "personalized therapeutic intervention" or "personalized medicine" [61].

Among the neoplastic diseases in which the immunotherapy method has found significant clinical application during the recent years, is melanoma (which has been described as the "flagship" of immunotherapy, because it carries many immune checkpoint inhibitors and is suitable for the application of various immunotherapeutic agents), lung cancer, kidney cancer, urinary bladder cancer and of course, gastric cancer. As it has already been mentioned, the monoclonal antibodies used to treat gastric cancers are those which inhibit the programmed cell death protein-1 (PD-1), the programmed death ligand-1 (PD-L1) and the cytotoxic T-lymphocyte antigen 4 (CTLA-4) [42]. To date, the pharmaceutical agents of "targeted therapy"

for gastric cancer that have received approval for clinical use by the U.S.A.'s Food and Drug Administration (FDA), are the following [40]:

- *Trastuzumab:* its action is based on the presence of overexpression of the Human Epidermal Growth Factor Receptor 2 (HER2),
- *Pembrtolizumab / Nivolumab:* both of them are PD-1 monoclonal antibodies and are approved as a combination therapy along with platinum and fluoropyrimidine-based chemotherapy for patients with advanced and / or metastatic gastric cancer,
- *Entrectinib / Larotrectinib:* both of them are tropomyosin receptor kinase (TRK) inhibitors and their use is based on testing of Neurotrophic Tyrosine Receptor Kinase (NTRK) gene fusions.

Xue and Xu, (2022) [62] published the results of a systematic literature review and meta-analysis regarding the efficacy of chemotherapy combined with the monoclonal antibody trastuzumab for the treatment of advanced gastric cancers which were positive for the Human Epidermal Growth Factor Receptor 2 (HER2 - positive). In this meta-analysis they included 18 randomized-controlled trial, with 1964 participants in total. The main conclusions of the study was that 1) The combination of chemotherapy along with trastuzumab was superior to that of chemotherapy alone for the treatment of HER2-positive advanced gastric cancers and 2) The addition of trastuzumab did not produce any statistical or clinical significant deterioration of the regimen's safety profile. These findings, according to the authors of the meta-analysis, are particularly encouraging for the results of new immunotherapy methods in the treatment of advanced gastric neoplasms.

Huang et al., (2021) [63] published the results of a systematic literature review and Bayesian network meta-analysis, regarding the safety and efficacy of the third-line treatments for advanced gastric cancer. In this systematic review the authors included 10 clinical trials with in total 3.012 patients with advanced gastric cancer. One of the main findings of the meta-analysis was that nivolumab, along with apatinib were the most effective treatments, with nivolumab having the best 1-year overall survival rate and also the best overall survival rate in patients with HER2 –positive gastric cancer, tumours of the gastroesophageal junction and tumours with no history of previous gastrectomy. Some of the main findings of this important systematic literature review and meta-analysis are summarized in Figure 21. According to the authors, it seems that in advanced stage gastric cancer, the immunotherapy regimens with the immune checkpoint inhibitors is the best third-line therapeutic option.

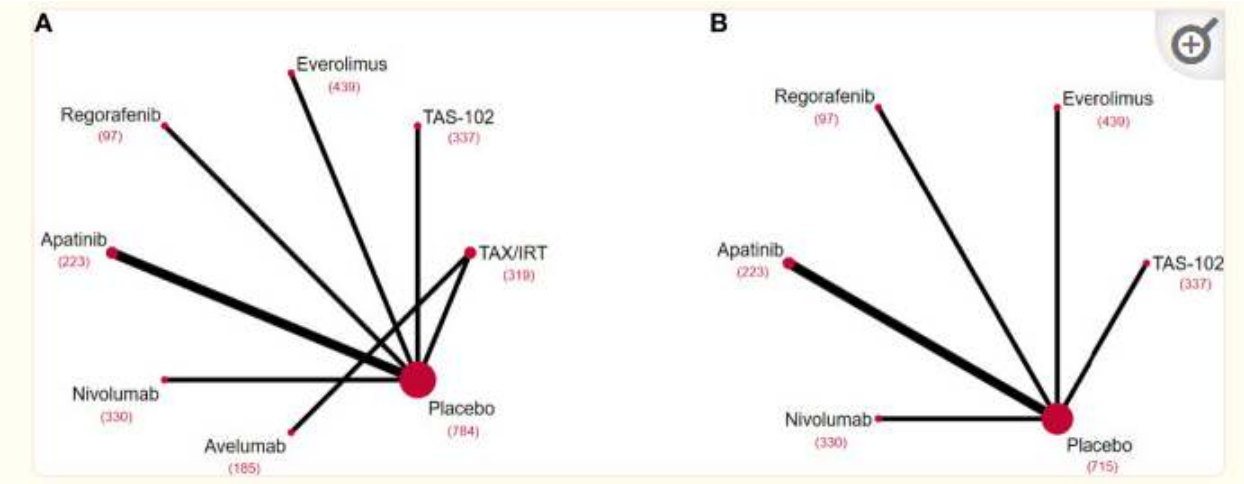

Figure 21: Third-line treatments for advanced-stage gastric cancers

(A): Overall survival. (B): Progression free survival. Nivolumab, along with apatinib were the most effective treatments, with nivolumab having the best 1-year overall survival rate and also the best overall survival rate in patients with HER2 –positive gastric cancer, tumours of the gastroesophageal junction and tumours with no history of previous gastrectomy. Source: Huang et al., (2021) [63].

Finally, in an in vitro study, Shon et al., (2021) [64], showed that the TRK inhibitor entrectinib had significant anti-tumour action, in the gastric cancer cells through the inhibition of various signalling pathways (especially the VEFGR and the NTRK signalling pathways).

Another field of immunotherapy for gastric cancer that in recent years has begun, after the experimental stage, to be applied in clinical practice, is the neo-adjuvant (preoperative) immunotherapy treatment for advanced gastric tumours. Just recently Xu et al., (2023) [65], published the results of a systematic review and meta-analysis (5 clinical trials with 206 patients in total), regarding the effectiveness of neoadjuvant immunotherapy for the treatment of advanced gastric cancers. The results of the study showed that this treatment option may prove to be particularly useful in the treatment of these difficult neoplasms; however, further research with phase III clinical trials is needed to establish beyond doubt both its efficacy and safety.

Table 3: Novel therapeutic options for gastric cancer

Author, Country	Type of Study	Participants / Intervention	Outcome measures / Results	Main Conclusions
Xue and Xu, (2022) [62], China	Systematic literature review and meta-analysis. 18 randomized-controlled clinical studies,	1964 patients with advanced, HER2-positive gastric cancer. Effectiveness of combined chemotherapy and trastuzumab treatment vs chemotherapy alone	Response rate, disease control rate, major side effects. RR: OR= 0.56, p < 0.003. DCR: OR= 1.61, p=0.004. No significant difference in major side effects	The combination of chemotherapy along with trastuzumab was superior to that of chemotherapy alone for the treatment of HER2-positive advanced gastric cancers, without any deterioration in the regimen's safety profile.
Huang et al., (2021) [63], China	Systematic literature review and Bayesian network meta-analysis. 10 clinical trials, phase II/III	3.012 patients with advanced gastric cancer. Immunotherapy treatment	One-year overall survival and progression – free survival rates mOS: apanitib (HR:0.61) and nivolumab (HR: 0.62), the most effective. mPFS: apanitib vs placebo: HR = 0.38. OS: nivolumab ranked 1st TAS-102 the most toxic treatment, POS, 1-year OS, ORR and PPFS: 5.1 months, 25%, 10% and 1.71 months respectively	Nivolumab, along with apanitib were the most effective treatments, with nivolumab having the best 1-year overall survival rate and also the best overall survival rate in patients with HER2 –positive gastric cancer, tumours of the gastroesophageal junction and tumours with no history of previous gastrectomy.
Xu et al., (2023), [65], China	Systematic review of pilot studies and meta-analysis. 5 pilot clinical studies	206 Chinese patients with resectable gastric tumours. Neoadjuvant (pre-operative) immunotherapy	Major pathological response rates, pathological complete response rates, adverse effects. pCR: 26.5% MPR: 49.05. Grade 3-4 TRAEs: 20.0%, Post-operative complications: 30.1%.	With the exception of grade III and IV adverse effects and complications, all the other outcome measures was in favour to the neo-adjuvant immunotherapy. It can be a particularly useful method in the treatment of these difficult neoplasms; however, further research with phase III clinical trials is needed to establish beyond doubt both its efficacy and safety.

C.2 Novel biomarkers under investigation and future novel therapies

Epidermal growth factor receptor (EGFR) is most probable τhe molecular biomarker that has been the subject of the largest amount of scientific research in recent years in terms of its association with stomach cancer. However, although the results of research on several other types of cancer are still promising, for gastric cancer, there is still no clear evidence of the effectiveness of inhibitors of EGFR (Table 4).

Okines et al., (2010) [66] published the results of the REAL-3 phase II-III prospective, multicentre, randomized-controlled study, showed that the addition of panitumumab, a human monoclonal antibody targeting EGFR did not improve statistically significantly the overall survival of 29 patients with advance esophagogastric cancer, who have been treated with the EOC chemotherapeutic regimen (epirubicin, oxiplatin and capecitabine).

Three years later, Lordick et al., (2013) [67] in a randomized-controlled, phase III clinical study (the EXPAND trial, involving 904 patients suffering from previous untreated advanced gastric cancer showed that the addition of the EGFR inhibitor cetuximab to the chemotherapeutic regimen cisplatin-capecitabine din not offer any substantial benefit to the survival of those patients.

On the other hand, more encouraging were the results of a more recently published study by Maron et al., (2018) [68], in a series of 7 patients with EGFR-amplified gastric tumours, who were treated, along with the standard chemotherapeutic regimens, with cetuximab (an EGFR inhibitor agent) as well; the results of this small case series showed that the patients' overall response rate was 58%, whereas the disease control rate was 100%, findings suggesting that the use of these agents may be effective in selected categories of patients with gastric cancer and merit further scientific study.

Another novel therapeutic agent that has been the subject of study in recent years is the monoclonal antibody Zolbetuximab, which binds to CLDN18.2 (claudin 18.2), a cell-surface protein which has been found to be expressed in the 40% of the HER-2 negative gastric adenocarcinomas [69]. Klempner et al., (2023) [70], published the results of the ILLUSTRO, phase II multicohort trial, which showed very promising results (both in its efficacy and in its safety profile) in patients with advanced and previously untreated gastric adenocarcinomas which are CLDN18.2 - positive, stressing the need for continued research into the efficacy of this new pharmaceutical agent.

Table 4: The inhibitors of the epidermal growth factor receptor (EGFR)

Author, Country	Type of Study	Participants / Intervention	Outcome measures / Results	Main Conclusions
Okines et al., (2010) [66], UK	Phase II-III prospective, multicentre, randomized-controlled study (REAL-3 trial)	29 patients with advanced esophagogastric cancer. Addition of the EGFR inhibitor panitumumab to the standard chemotherapeutic EOC regimen	Survival and toxicity	The recommended dose for EOC + p is epirubicin 50 mg/m^2, oxaliplatin 100 mg/m^2, capecitabine 1000 mg/m^2/d and P 9mg/kg, every 3 weeks.
Lordick et al., (2013) [67], Germany	Phase III randomised-controlled multicentre trial (EXPAND trial)	904 with advanced, previously untreated gastric cancer. Addition of cetuximab to the standard regimen cisplatin-capecitabine	Progression free survival rates, side effects. Median PFS: 4.4 months vs 5.6 months (p = 0.32) Grade 3-4 adverse events: 83% vs 77%. Grade 3-4 skin reactions: 54% vs 44%	The addition of the EGFR inhibitor cetuximab to the chemotherapeutic regimen cisplatin-capecitabine did not offer any substantial benefit to the survival of those patients.
Maron et al., (2018) [68], USA	Case series	7 patients with advanced gastroesophageal carcinoma. Addition of EGFR inhibitors in EGFR-amplified gastroesophageal carcinoma.	Objective response, disease control, progression free survival. OR: 58%, Disease control 100%, median progression free survival: 10 months	The patients' overall response rate was 58%, whereas the disease control rate was 100%, findings suggesting that the use of these agents may be effective in selected categories of patients with gastric cancer and merit further scientific study.
Klempner et al., (2023) [70], USA	Phase II multicohort trial (ILLUSTRO)	CLDN-18 positive patients with gastric adenocarcinoma. Efficacy and safety of Zolbetuximab	Objective response rate, overall and progression free survival rates, clinical significant adverse effects. Cohort 2 (Zolbetuximab + mFOLFOX6: ORR: 71.4%. Median PFS: 17.8 months. Gastrointestinal adverse effects: 63% - 90%.	The addition Zolmetuximab had promising results, with no deterioration of the regimen's safety profile. Further research is needed.

D. Conclusion

Gastric cancer is a very important health problem in all regions of the planet, which is of concern to health systems in all countries of the world. In a large percentage of cases, it is not diagnosed in time, with the end result being that the disease is accompanied by high morbidity and mortality rates. Among the most important risk factors for the development of the disease are helicobacter pylori infection, smoking and chronic dietary habits, such as excessive salt consumption in the diet. In any case, genetic factors seem to play an important role in its development, with genetic testing now considered necessary in cases of people who have a burdened hereditary history.

The revised clinical practice guidelines for the treatment of gastric cancer, published by the National Comprehensive Cancer Network (NCCN) in 2022 [40] pay particular attention to the multidisciplinary treatment of the disease with the cooperation of scientists from different disciplines in order to achieve the best possible outcome for the patient. Continuous monitoring and support of the patient is essential at all stages of the disease; however, special care is needed for patients with advanced disease, which has relapsed or has given rise to distant metastases that are deemed unresectable, and who need the maximum supportive care. In these cases of advanced disease, the maximum of symptomatic and palliative treatment should be ensured, without it being necessary in all cases to combine it with systemic treatment of the disease (chemotherapy, radiotherapy or a combination of both modalities).

Based on the most up-to-date literature data, the recommended therapeutic approach, especially in patients with good physical condition and local disease, includes surgical resection of the primary lesions with margins >5 cm, D2 (extended) lymph node dissection without pancreatectomy and splenectomy only when the spleen is involved by the disease. Nowadays, in patients with local-peripheral gastric cancer, international guidelines recommend peri-operative (neo-adjuvant and adjuvant) chemotherapy; this approach improves overall survival. The chemotherapy regimens used are generally well tolerated, with the majority of patients managing to complete both pre- and post-operative chemotherapy without major complications and side-effects.

With the continuous development of scientific research in this field, in recent years targeted therapeutic interventions have given new hope in the effort to treat advanced gastric cancer. Thus, the recently published NCCN clinical practice guidelines in Oncology for gastric cancer [40], include the following:

- In patients with HER2-positive tumours, chemotherapy plus trastuzumab is recommended as 1st line therapy,
- In patients with PD-L1 expression, chemotherapy plus nivolumab is recommended as 1st line therapy,
- For patients with metastatic gastric cancer, ramucirumab should be considered as an effective 2nd line therapy,
- For patients with MSI-H/dMMR or TBM-H tumours, ramucirumab and / or pembrolizumab should be considered as 2nd line, or subsequent therapeutic options.
- For patients with NTRK gene fusion-positive tumours, Larotrectinib or Entrectinib are recommended as 2nd line therapy.

Advances in the application of new therapies, such as immunotherapy, targeted therapies, gene therapies, vaccines, drug combinations and deciphering pathways previously unknown with the help of molecular biology, immunology and technology development, allow us to be optimistic about the long-term survival and/or cure of cancer patients who currently have an unfavourable prognosis. Scientists from many disciplines are working intensively in this direction to make the dream of a "cure" a reality. In all cases, it is essential to continue scientific research by encouraging patients with gastric cancer to participate in clinical trials in order to prove the efficacy and safety of the existing therapeutic regimens and to study novel - innovative treatment options.

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