Molecular Pathology in Gastric Cancer: Implications for Surgical Treatment

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ABSTRACT

Gastric Cancer is one of the major causes of death due to cancer related deaths with the main surgical treatment being the primary management approach. Due to the application of modern molecular pathological features, understanding of GC has improved remarkably consequently leading to better management of the disease. Some of the key molecular markers that are include HER2, microsatellite instability or MSI and CDH1 mutations. It was also established that these markers help identify between total or partial gastrectomy as to which type of surgical method should be adopted. The paper is thus about the review of the uses that molecular profiling for gastric cancer, in particular in setting up the surgical intervention and stratifying the patient. It focuses on how and where medicines, precision medicines, and AI can affect the innovations on the surgical practice.

Keywords: Gastric Cancer, Molecular pathology, HER2, Microsatellite instability (MSI), CDH1 mutations, surgical treatment, total gastrectomy, precision medicine, targeted therapies, bio-markers-driven surgery, personalized treatment, patient stratification.

Introduction

Gastric Cancer (GC) is the fifth most common cancer across the globe and occupies the third place among cancer deaths. Its significant burden is in East Asia, as well as in Eastern Europe. Even though, there are improvements perceived in early detection but the Gastric Cancer late-stage diagnoses that are responsible for this very poor prognosis. The significant concern in GC is the contribution of molecular pathology in improving diagnostic, prognostic, and particular approaches toward treatment given the genetic and epigenetic changes occurring in GC. In this,

one of the identifying aspects of individualizing the approaches to the surgical treatment is the determination of the molecular markers. That could also enhance the result by defining as far as the resection is concerned, along with the adjuvants treatment. The paper aims to analyze the relationship between molecular pathology in GC and improving its surgical management.

Literature Review

Molecular Pathology of Gastric Cancer

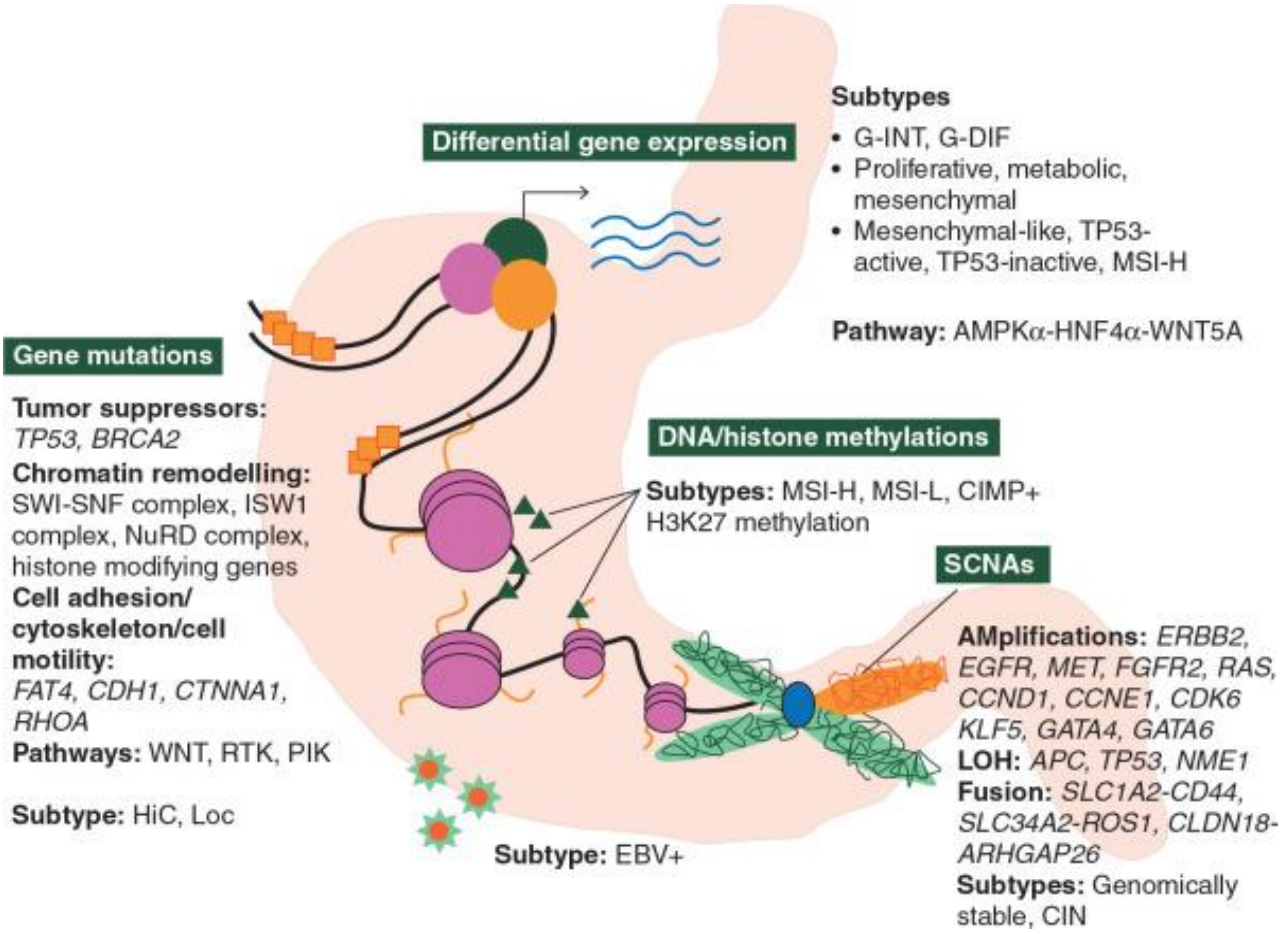

Figure 1: Genetic and epigenetic modification of gastric cancer (GC)

(Source: Chia, and Tan 2016)

According to Chia, and Tan 2016, in this research paper the author discussed about the life expectancy of the patient with gastric cancer depends on histological and molecular characteristics. These factors are important for diagnosis and further therapy. The World Health Organization (WHO) classify the gastric cancer into tubular, papillary, mucinous, and poorly cohesive carcinoma, including the signet-ring cell carcinoma. It provides more details about the

shape of the tumor but not concerning molecular differences (Chia, and Tan 2016). GC is classify into four molecular subtypes and they are Epstein-Barr virus (EBV) Positive, this categories by PIK3CA mutations and PD-L1/2 overexpression. Microsatellite Instability(MSI)high, GS associated with CDH1/RHOA mutations and diffuse GC; and CIN with TP53 mutation and HER2 strengthening more on sub classification of the molecular basis of subtypes of GC improves the patient's stratification which in turn affects the type of surgical intervention as well as a targeted therapy. Incorporation with the WHO and TCGA classifications improves the focus on precision medicine in the context of GC patient's management.

Biomarkers in gastric cancer

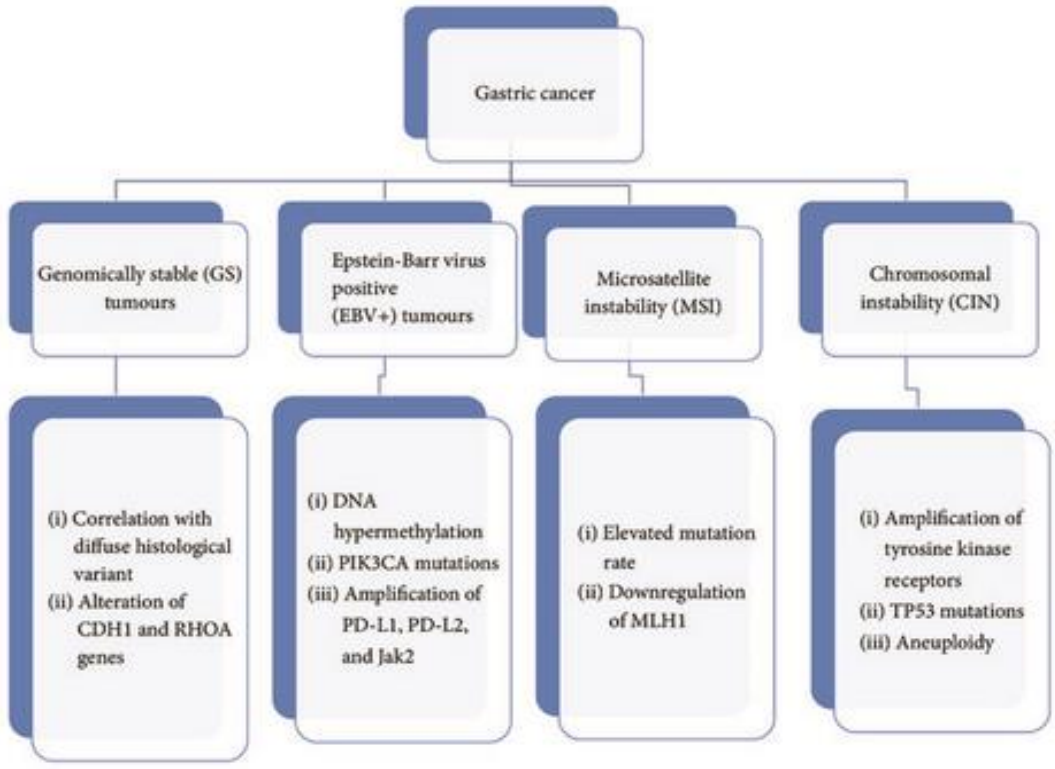

Figure 2: Based on genomic features the Gastric Cancer Categories

(Source: Carlomagno*et al*.2017)

According to Carlomagno*et al*.2017,in this study the discussion is based on the Biomarkers, which play an important role in the prediction of the disease and the response of gastric cancer to

therapy. This study identifies those early diagnosis biomarkers of gastric cancer, as well as the general response of gastric cancer patients to the respective treatments in their course of treatment. Gastric cancer HER2 amplification is in about 20% of GC cases and may exploited for more aggressive tumor characterizes with the use of trastuzumab (Carlomagno*et al*.2017). This PD-L1 of GC is relate to MSI or EBV positivity, which suggests the effectiveness of immunotherapeutic agents such as pembrolizumab. CDH1 gene mutations are recognize for diffuse type GC and are relate to rather poor prognosis and HDGC, which may treated with prophylactic gastrectomy. Molecular markers include VEGF, MET, and FGFR2 some of which are relevant to therapy. Incorporation of these molecular markers within the clinical context helps in the patient classification and offers a framework on which treatment individualization can occur, for instance regarding surgical procedure and pharmacological therapy. Targeted therapy integration in the treatment of GC increases the understanding of biomarker-associated therapeutic strategies in surgical and systemic treatments.

Histopathological Classification and Molecular Subtypes

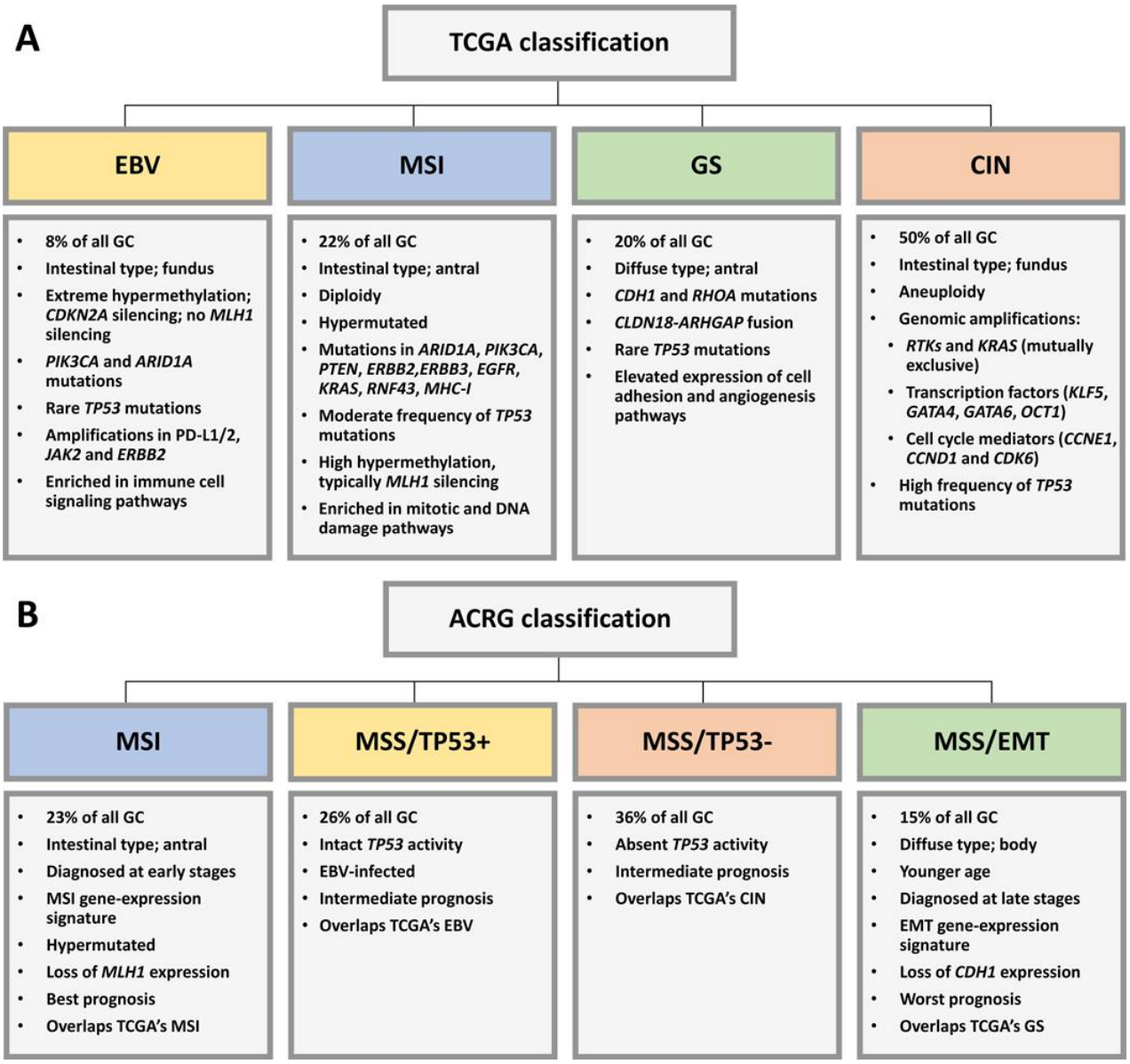

Figure 3: Gastric Cancer classification

(Source: Figueiredo*et al*.2017)

According to Figueiredo*et al*.2017,the research is based on regarding the Gastric cancer involves genomics or phenotype changes that make it crucial for the development of tumors development, prognosis and response to treatment. The HER2 amplification is involved in few GC cases. However, it is associated with tumor aggressiveness and the response to trastuzumab. MSI thus signifies a molecular subtype linking the condition with a good prognosis and

sensitivity to immunotherapy resulting from defects in DNA mismatch repair (Figueiredo*et al*.2017). The best-known genetic changes involving GC are mutations in TP53 gene, which in turn leads to genomic instability and cancer progression. Other main changes include CDH1 alteration in diffuse-type Gastric Cancer and aberrant methylation of tumor suppressor genes (Figueiredo *et al*.2017). These molecular alterations assist in the classification of GC, determination of prognosis, and management of surgery, which supports the use of PM in treatment plans.

Surgical treatment approaches

TCGA gastric cancer subgroups	Frequency (%)	Main characteristics
Epstein–Barr virus (EBV)	9	Gastric fundus location CDKN2A silencing Hypermethylation of CpG islands Over-expression of immune-checkpoint ligands
Microsatellite instability (MSI)	22	Body and pyloric gastric location Correlation with Lauren intestinal subtype Hypermutation status MLH1 silencing and hypermethylation of CpG islands
Genomically stable (GS)	20	Homogenous distribution to all portions of the stomach Correlation with Lauren diffuse histology CDH1 and RHO mutations, CLDN18–ARHGAP fusion
Chromosomal instability (CIN)	49	Homogenous distribution to all portions of the stomach Correlation with Lauren intestinal histology Activation of RAS pathway Mutation of TP53

Figure 4: Based on TCGA, the gastric cancer type with frequency and molecular features

(Source:Ratti*et al*.2018)

According to Ratti*et al*.2018,the study is research and discussed about theSurgery treatment, which is the keystone of GC management and technical advancement will ensure that it remains in relation to the molecular classification of tumors. The two main forms of respective procedures of the stomach remain both total and subtotal gastrectomy and therefore D2 lymphadenectomy belongs to both. Totally or subtotal approach used depends with the location of the primary tumor and with the molecular characteristics of the tumor as well. Generalizing from the MSI-high tumors, it reflects that immune checkpoint inhibitors have improved sensitivity and may require less radical surgical procedures for treatment (Ratti*et al*.2018). HER2-positive GC should manage step wisely and in most of the cases, surgery is combine with

treatment using trastuzumab (Ratti*et al*.2018). Patients with CDH1 gene mutations that relate to familial HDGC require undergoing prophylactic gastrectomy since they are prone to the development of the disease with odds of metastasis. The importance of laparoscopic and robotic-assisted surgeries is important to provide many least invasive choices with significantly less risk in an early stage and biomarker-driven cases. Molecular profiling has developed to reach a level where the approach of making surgical approaches are becoming more precise shift towards the biology-driven and patient-specific surgery. This advancement maximizing the patients' outcome, supporting the significance of the concept of precision-surgery in cancer treatment.

Methods

Research design

In this research, the collection of secondary data analysis is use by assessing the role of molecular pathology in gastric cancer and its implication on the surgical management of the disease. For the review, PubMed, Google Scholars use to systematically search for English, peer-reviewed articles that focus on molecular biomarkers, histopathological classification and surgery from 2010 to 2018. The identification of the sources of data is obtain from three main sources consisting of PubMed, Google Scholar, and Science Direct. This ensure that the high impact of journals and clinical studies is included in the research study (Van Cutsem*et al*.2016).The research criteria use selection procedures identifying research that distributed on genetic and epigenetic changes, biomarker guided treatment approach, and molecular profiling in the decision making of surgery. The method provides a thorough and evidence based understanding of the importance of molecular pathology in gastric cancer surgery.

Data collection

To collect the data for this study, Secondary sources had review in this paper to obtain the relevant data and information. Sources include articles in the peer-reviewed journals, clinical trials and analyses from 2010 to 2018.Recent literature on molecular pathology, biomarkers and surgical therapy for gastric cancer is obtain from the databases that include PubMed, Google scholar and Science Direct. The words that would work when searching for the data, gastric cancer, molecular pathology, biomarkers, surgical treatment, precision oncology (Hu *et al*.2012). This review is based on essential, methodologically sound, and clinically relevant chosen papers.

Thus, the search is conducted to provide a list of a large amount of high relevancy and quality data by excluding reports that are clinician also the molecular-clinical-surgical irrelevant.

Data Analysis

The collected data is analyse using a qualitative analysis of the collected secondary data, focusing on current situations, relationship and patterns of molecular pathology and its association with surgery for gastric cancer. They were published based on the biomarkers, HER2, MSI, and CDH1, the histopathological classification, as define by the WHO and TCGA, and surgical management approaches. The described comparisons would help reveal how molecular profiling affects such decision-making in surgery, include the resection, boundaries and application of personalize therapies (Correa*et al*.2010). These findings for conformity, clinical utility, and relevance to help the clinician. It would therefore ease an all-round understanding of how molecular pathology is beneficial in enhancing the treatment of gastric cancer surgery.

Results

The Key Molecular markers influence the surgical decisions

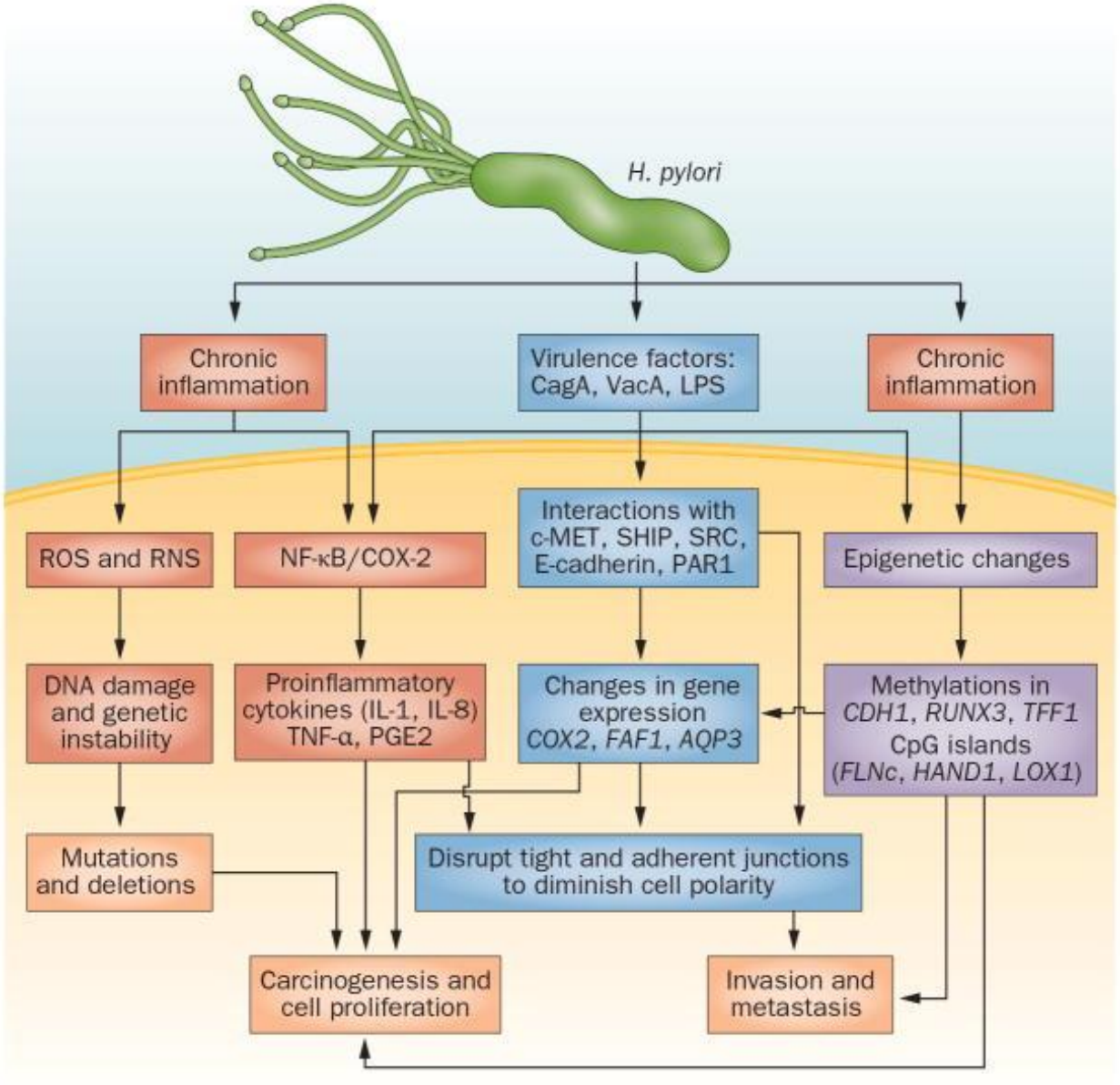

Figure 5: Helicobacter pylori's molecular carcinogenesis in gastric cancer

(Source: Wadhwa*et al*.2013)

The subtypes are based on molecular marker play a very significant role in the handling of gastric carcinoma surgery. HER2 overexpression, it is present in almost 20% of the cases of BC and affects treatment by involving trastuzumab in the surgical process. They also found that the MSI-high tumors have favorable prognostic implications and incline to treat by less extensive

surgery. CDH1 mutations are recognize to increase the risk of developing HDGC and it is the only preventive therapy for this disease total gastrectomy (Wadhwa*et al*.2013). It is regarding the problem of resection, the further development of the tumor is potentially dependent on the presence of TP53 mutations. It may even help in pre-surgery planning since the kind of resection or additional therapy that will follow may also decide based on this knowledge.

Role of molecular pathology in patient stratification for surgery

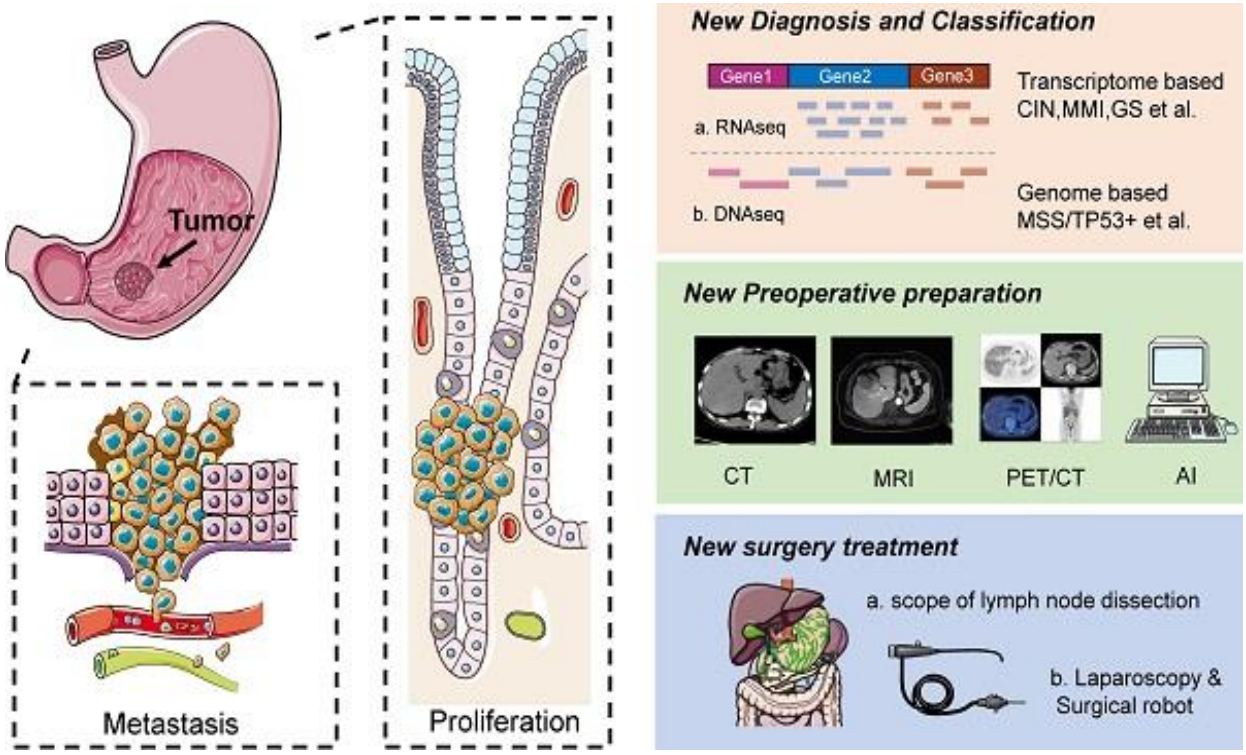

Figure 6: Advances in gastric cancer surgery during medicine era

(Source: https://www.ijbs.com/v17p1041.htm)

The molecular pathology is an essential factor for the management of GC since it helps to categorize patient for surgery. High MSI tumors should not completely resected. CIN-related tumors that are mostly associated with TP53 mutation should be radically remove. CDH1 gene mutations associated with HDGC have high metastatic propensity. Thus, total gastrectomy is advice in prevention (Rugge*et al*.2014). Immunotherapy is add to surgery when associated with EBV-positive tumors or PD-L1 expression may suggest the value. Such molecular information has proved rather useful in directing the kind of surgery to provide to the patients along with the outcome of that particular surgery on the disease in the management of GC.

Analysis of surgical outcomes based on molecular characteristics

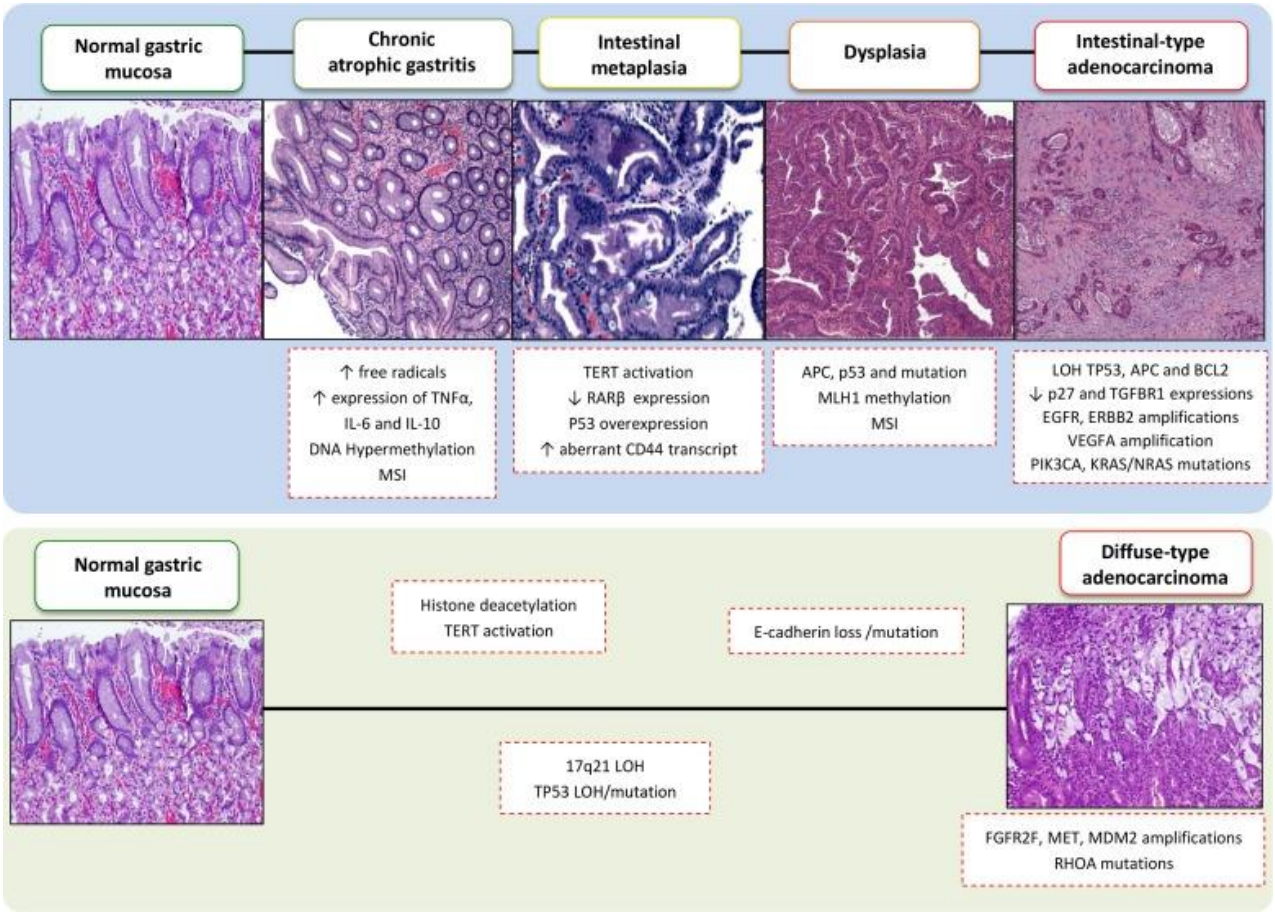

Figure 7: The sequence and particular order of molecular events in GC

(Source: Riquelme*et al*.2015)

From this, the molecular features of gastric cancers will impacts survival outcomes in very significant ways even after resection. This study identify that MSI-high cancers had an advantageous outcomes after surgery with less recurrences and could possibly require fewer aggressive surgery. It is acknowledge that HER2-positive GC is associated with disease that is more aggressive but it is more amenable to treatment through various forms of surgery with drugs derived from trastuzumab (Riquelme*et al*.2015). Although subtotal gastrectomy is done, CDH1-mutated diffuse GC almost never has improved prognosis by it and must operate by total gastrectomy only. Metastatic EBV-positive patients, who have immune active and influenced tumors will likely to have longer survival time after surgery, therefore will benefit a lot from immunotherapy. The consequently developed results pointed toward the fact that failure in the

use of molecular-guided surgical action plans would be critical to proper treatment outcomes and patient survival rates.

Discussion

From the analysis of the results, it can identify that molecular pathology have the key role in determining the further treatment plan of gastric cancer by means of an operation. Molecular profiling therefore aids in the decision-making as to when a total or subtotal gastrectomy is need, because of the differences between the specific mutated CDH1 cases, in which a total gastrectomy is normally indicate in most cases, and the MSI-high tumors for which less invasive surgeries are permissible (Jang, and Kim2011). There are several disadvantages associated with it such as the variation observed in the molecular testing done alongside, number of large-scale studies, natural accretion of the experience and biomarker based protocols. There is a need to advance further research in the field through combining methods of molecular pathology with intraoperative decision-making. The following are the ways through which the treatment of GC is maximize and the prognosis of long-term survival improved personalize surgery. Molecular profiling is one of the newest methods that seek to enhance the treatment of GC and other ailments.

Future directions

The newer molecular biomarkers as if MET amplifications along with the mutations in FGFR2 might give further sharpened surgical decisions and treatment that is even more individual. These progresses continue to move forward in refining the targeted therapies to direct the degree and outcome of surgery for the tumors with HER2-positive and MSI-high status (Gullo*et al*.2018). Moreover, with AI into molecular diagnostics of cancer the planning of surgery can change in the following ways, real-time features of the gastric of tumor, improved methods of resection, and the prognosis of the patient. As for the future works of this field, it would be revealing in what ways these advancements could integrated to improve the particularized management of gastric cancer surgery.

Conclusion

The role of molecular pathology in the management of Gastric carcinoma is a very essential factor that determines the surgical solution. These include HER2, MSI, and mainly CDH1 mutations, thus enabling a better management of total vs partial gastrectomy. The number of

publications has risen in current studies. However, some limitations have to address and include development of a universal molecular testing protocol, and conducting further larger validation study. Some of these biomarkers may advance the process of surgical planning at an advanced level such as precision medicine as well as artificial intelligence. Gastric cancer surgery may also progress gradually to further refine such dreadful surgery to establish more appropriate therapeutic strategies according to its molecular signature, with desirable outcomes of enhancing improve survival and life quality of gastric cancer patients.

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