



Insights into Gastric Cancer

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ABSTRACT

Gastric Cancer (GC) is one of the serious diseases prevailing globally. GC has immense global life-threatening health issues by taking 4th place among all the widespread cancers and 2nd foremost reason for fatality around the globe. Numerous patients have inoperable disease at diagnosis or have recurrent disease after resection with curative intent. In the present review, we have put forward all the possible advanced treatments for GC, which includes the application of Nanotechnology, Monoclonal antibodies, and Robotic surgery. Nanoparticle offers a potentially improved treatment of multidrug-resistant cancers. GC is uniquely positioned as an area of research for targeted and nanoparticle therapies. This review briefs about design and considerations to develop targeted nanoparticle-based approaches for overcoming physiological hurdles in GC treatment. Based on current knowledge, molecular and cellular mechanisms, a number of novel biologic approaches such as monoclonal antibodies have been recently introduced for cancer treatment that mainly affects the immune system or target signaling pathways playing a role in cancer and metastasis development. Surgical robotic systems have been presented into the area of GC therapy as an enhanced technology that has overwhelmed the technical limits of laparoscopy. A note is added to relevant studies dealing with treatment concepts and gives an overview of the latest trends and developments in the treatment of GC.



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INTRODUCTION

Gastric Cancer (GC) is one of the serious diseases prevailing globally. GC is an immense global life-threatening health issue, which takes the fourth place among all the widespread cancers and also

the second foremost reason for death around the world. Each year over 950000 new cases are identified globally. In 2012, the death rate was found to be nearly 720000 due to this deadly cancer. Figure 1 represents the anatomical classification of gastric cancer.

World widely GC is one among the 4th utmost widespread cancer occurring in males subsequent to lung cancer, prostate cancer, and colorectal cancer and the 5th utmost widespread cancer occurring in females following breast cancer, cervical cancer, colorectal cancer, and lung cancer. The quotient to develop GC in males is double as likely in females (10.9 v/s 5.5 per 100,000) with a peak age occurrence of 60–84 years. Technologically advanced screening activities are required, as is an advancement in diagnostic analysis of GC. GC tends developing deficiency of efficient screening approaches over 50% of patients to stand in advanced GC stages dur-

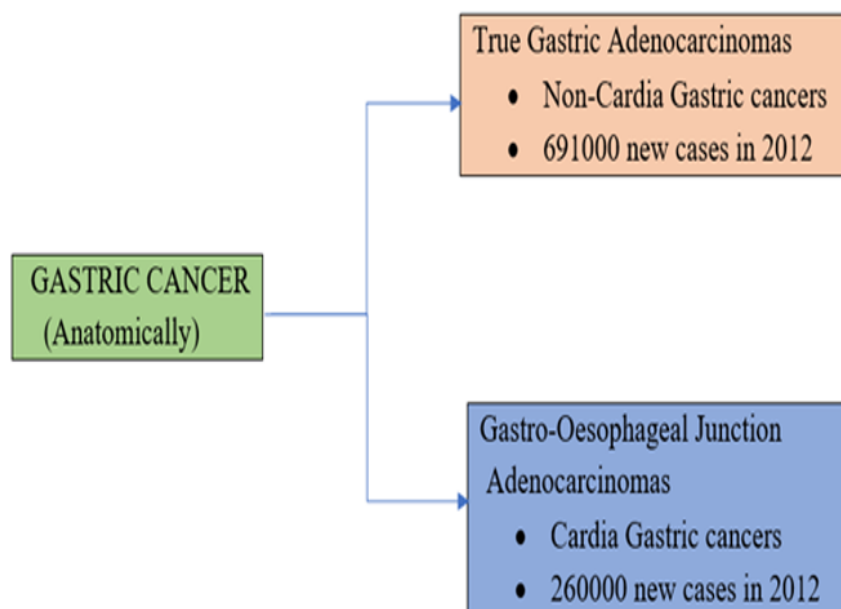


Figure 1: Flow Chart - Types of Gastric Cancer

ing preliminary diagnosis and at this point, many of these patients don't hold the chance for fundamental surgery and are unwilling to take treatment through adjuvant treatment.

A newly evolving body of evidence confirmed that mAb therapy could be an effective treatment in tumors. Using mAbs as monotherapy or adjuvant therapy is increasing in different types of cancer to achieve survival benefits and more efficient treatment. Hybridoma technology developed by Kohlen and Milstein paved the way for mAbs productions and made initial significant changes in clinical oncology.

In this review, the advancement in nanoparticles in the field of cancer is discussed as they emerge as an innovative therapy. Nanoparticles provide the potential for improved possibilities and enhanced therapy of multidrug-resistant cancers. Firstly, the overall mechanism of nanoparticles will be briefed. In addition, an emphasis on the newer technology used to overcome GC is been introduced (Vyas *et al.*, 2014). In this review, an effort is put to discuss the overview of GC, risk factors, treatment approaches and their utilization in the treatment of GC. Figure 2 provides detailed outcomes of the Gastrointestinal Oncology Conference held on September 29th, 2017, at Hershey country club, US (Siegel *et al.*, 2017).

Etiology

The utmost vital reason for sporadic distal GC is *Helicobacter pylori* (*H. pylori*) infection. In prolonged inflammation brought by infection of *Helicobacter pylori* and the subsequent carcinogenesis, together with host, bacterial, and environmen-

tal aspects, interrelate to enable damage restoration. Apoptosis (Cell death), the Modified proliferation of cells and few epigenetic alternations to tumor suppressor genes may take place, which can finally cause inflammation linked oncogenesis. *Helicobacter pylori* are a kind of bacteria that evade the human body and live in the gastrointestinal tract. After several years, these bacteria could form sores in the stomach lining or the lining of the small intestinal upper part. These sores are termed as ulcers. In a few individuals, an infection can cause GC. Infection with *Helicobacter pylori* is common. Nearly the world's two-thirds population has such kind of bacteria in their bodies. It doesn't lead to ulcers or any other symptoms in many individuals (Wang *et al.*, 2014), (See Figure 3).

Epstein-Barr virus is another pathogen-related to GC. This infective agent is found in cancer cells but absent in regular epithelial cells. This infective agent is seen in cancerous tumor cells of 80% of gastric carcinomas having lymphoid stroma. The part of the Epstein-Barr virus in carcinogenesis is still uncertain (Wang *et al.*, 1999), (See Figure 4).

Of all the GC cases, about 10% are associated inside family lines. Inherited case studies are assumed to occupy 1-3% of all GC cases. They comprise of 3 foremost syndromes like Gastric adenocarcinoma and proximal polyposis of the stomach, Familial intestinal GC and Hereditary diffuse GC. About 40% of families suffering from Hereditary diffuse GC show a hereditary basis-causative alteration in the CDH1 (Cadherin 1) and also caused by Mutagenesis in CTNNA1 (Catenin alpha 1). GCs are iden-

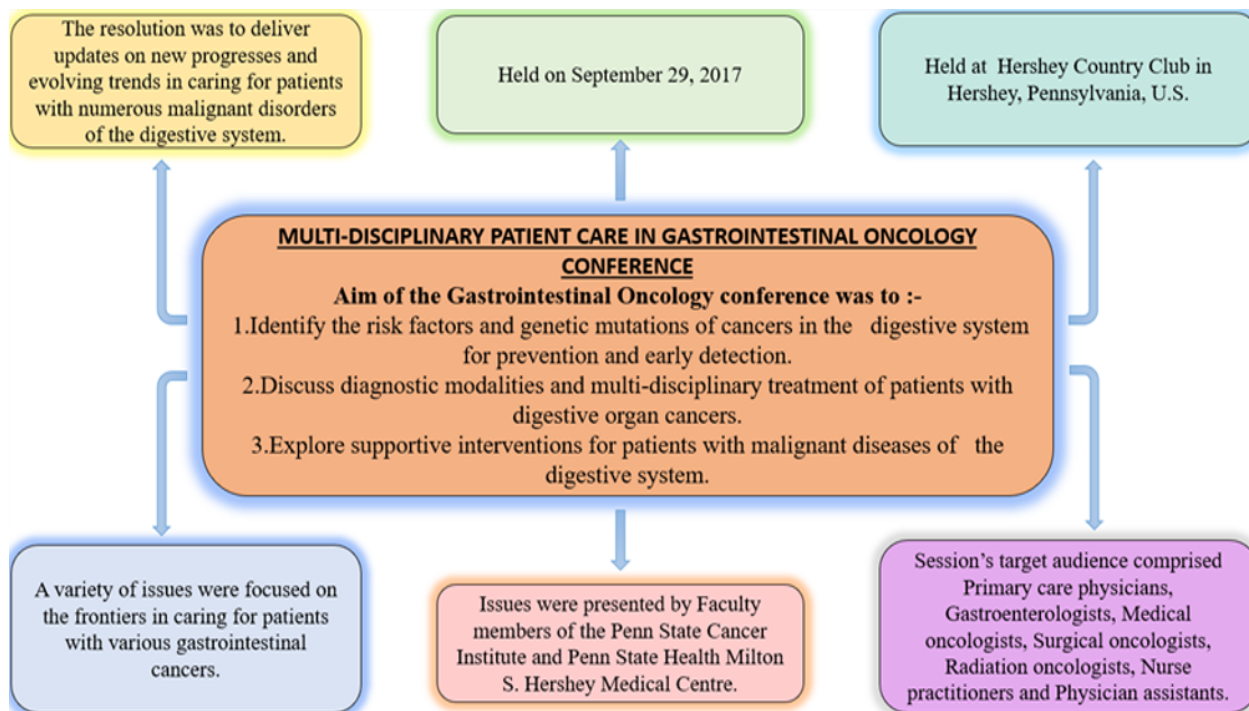


Figure 2: Gastrointestinal Oncology Conference

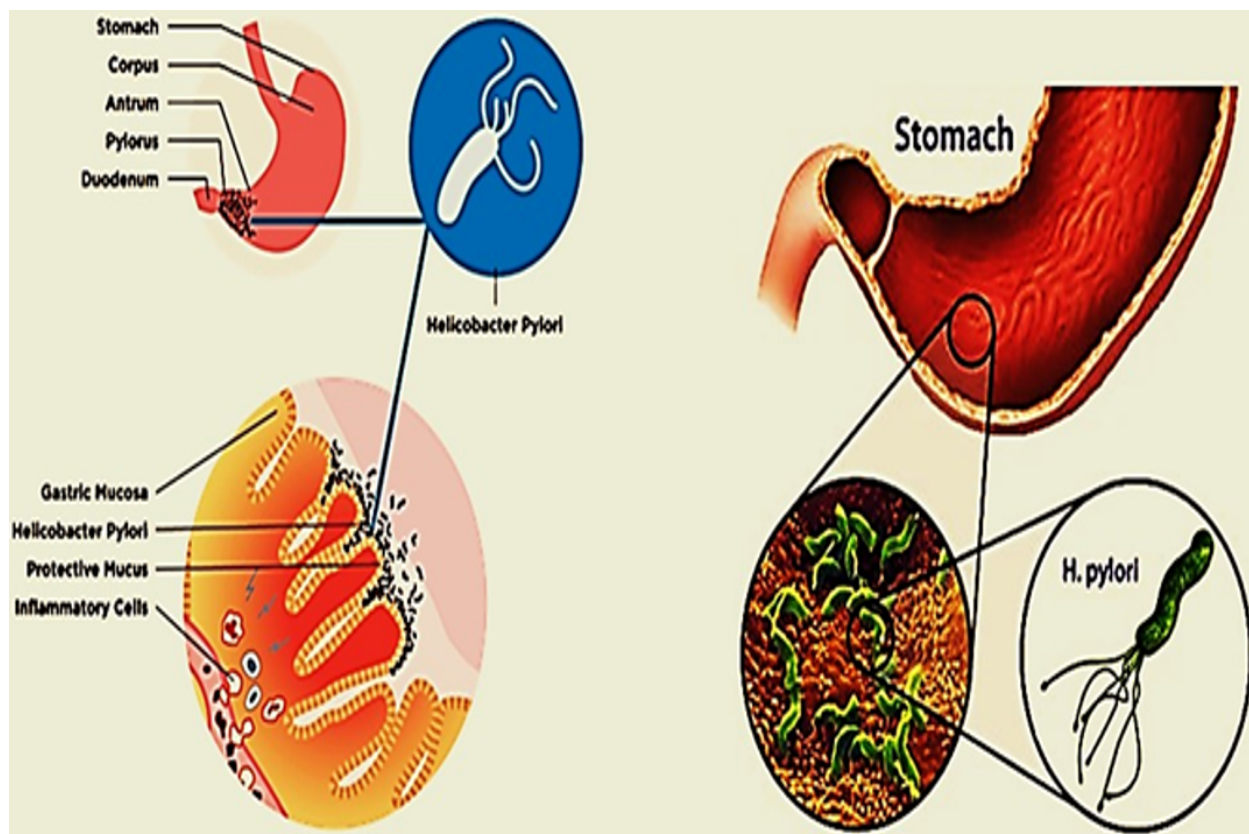


Figure 3: A: Helicobacter Pylori in the stomach. B: Helicobacter pylori that grow spirally in the mucous layer lining the inside of the human stomach

tified in individuals with mutations in TP53 (Li-Fraumeni syndrome), STK11 (Peutz-Jeghers syndrome), or APC (familial adenomatous polyposis). Poor intake of vegetables and fruits, more consumption of nitrates, pickled foods, salts and also smoking have been accompanying an elevated chance for GC. Even Obesity can be a risk aspect for GC.

Classification of Gastric Cancer

Gastric Cancer is a broad term encircling multiple malignancies of varying histology and comprises as mentioned below,

1. Adenocarcinoma
2. Lymphoma
3. Gastrointestinal stromal tumors (GIST)
4. Squamous cell carcinoma
5. Carcinoid tumors
6. Adenocanthoma.

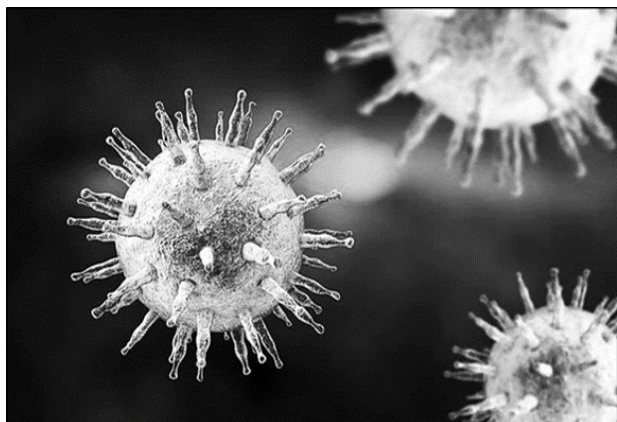


Figure 4: Epstein-Barr virus linked to stomach cancer

Adenocarcinoma

It is most common, which accounts for >90% of GCs. The Lauren system histopathologically categorizes gastric adenocarcinoma and divides the tumor into two types,

1. Diffuse
2. Intestinal.

Diffuse gastric adenocarcinoma

It tends to progress in younger patients and spreads by direct, transcoelomic and lymphatic routes, often resulting in peritoneal disease. A characteristic of this is Submucosal infiltrative growth. It produces a rigid, leather-bottle stomach known as "Linitis Plastica," which can last up to 14% of advanced gastric malignancies.

Intestinal gastric adenocarcinoma

It tends to occur in an older population and affects men more commonly (Male: Female ratio 2:1). It is common in endemic regions, accompanying environmental factors, atrophic gastritis and preferentially spreads hematogenous and typically resulting in liver metastases. Macroscopically, diffuse cancers appear as ulcerating lesions endoscopically, whereas intestinal tumors tend to be exophytic, bulky lesions (Laurén, 1965).

Lymphoma

It occurs in the lymphatic system, a part of the germ-fighting network of the human body, which includes the thymus gland, spleen, bone marrow and lymph nodes (lymph glands). The main subclasses are Hodgkin's lymphoma and Non-Hodgkin's lymphoma.

Gastrointestinal stromal tumors

GIST's are rare tumors occurring in very early forms of special cells, called the interstitial cells of Cajal (ICC) located in the wall of the GIT. ICC are cells of the autonomic nervous system that controls body functions such as digestion of food. ICCs are occasionally termed as the "pacemakers" of the GIT since they give signals to GIT muscles for contraction activity in order to transfer food particles and liquids along the GIT.

Squamous cell carcinomas

Squamous cells are flat cells present in the lining of few areas of the anal end portion and the oesophageal superior portion. Cancers initiating in such cells are known as Squamous cell carcinomas.

Carcinoid tumors

These tumors are a kind of neuroendocrine tumor, typically start in the lungs or the GI tract. They secrete hormones into the human body leading to signs and symptoms, for example, skin flushing or diarrhea.

Adenoacanthoma

It is a malignancy of squamous cells that have differentiated from epithelial cells. It can be present in the endothelium of the uterus, mouth and large intestine (American Cancer Society, 2017).

Risk Factors for Gastric/GEJ Cancers

Numerous harmful aspects were recognized that cause GC like Epstein-Barr virus, Obesity, Helicobacter pylori infection, Dietary aspects like pickled food consumption and red meat and High consumption of salt. A 43% rise in the danger for GC was linked with the consumption of processed red meat. 17.9% of individuals infected with GC have shown the presence of Epstein-Barr virus-encoded

small RNA (Wang *et al.*, 1999). The probability of death due to GC was found to be 6 –times greater in individuals diseased with H. Pylori compared to individuals having no infection (Wang *et al.*, 2014).

Environmental Factors

H. pylori infection

Gastritis caused due to infection with H. pylori infection, is known as the major reason for GC. Microbial resistance brought about the progress of vaccination methods to keep H. Pylori Infection in control. But these procedures are unsatisfactory until today. Dietary salt is also a vital aspect that leads to the progress of GC in H. pylori-infected individuals, by promoting H. pylori colonization along with enhancement of CagA (Cytotoxin-associated gene A) expression in H. Pylori (Ogura *et al.*, 2008).

Occupational risk aspects

GC may develop upon exposure to agents like N-nitroso compounds, Asbestos, Nitrogen oxides, Ionizing radiation, Cigarette smoking and Low consumption of vitamins A and C. It's defined in Chart 1,



Chart 1: Flow Chart

Genetic Factors

Modifications in the arrangement of DNA, either by hereditary or acquired, could lead to oncogenic pathway stimulation, directing to the progress and development of cancers. Approximately 40% of hereditary GC's harbour transmuted CDH1, which leads to faulty or declined E-cadherin expression, which would lead to the stimulation of EGFR (Epidermal Growth Factor Receptor).

Somatic mutations

Variability in chromosomes comprises a modification in chromosomal numbers that may vary areas in designated chromosomes, which might lead to transformed gene expression. Intestinal GC is connected with acquiring a copy number of chromosomal regions 20q, 17q, and 8q. This leads to greater expression of c-ErbB2 and EGF (epidermal growth factor). Diffuse GCs are connected with acquiring

copy number at 13q and 12q areas of chromosomes and subsequent FGFR overexpression (fibroblast growth factor receptor), HER2 (Human epidermal growth factor receptor 2) overexpression along with c-myc overexpression. Therefore, GC patients exhibiting HER2 overexpression can be efficiently cured with trastuzumab, a mAbs focused against HER2 (Mclean and El-Omar, 2014).

Table 1 explains various risk factors related to the progress of GC (Sjödahl *et al.*, 2007), and Table 2 is regarding the Worldwide prevalence of the most important types of gastrointestinal malignancies and related mortality rate (Ferlay *et al.*, 2010).

The Role of Nanotechnology in Gastrointestinal Cancer

Nanoparticles possess a size range of nanometres that have the ability to carry loaded active drugs to cancer cells, enhancing the specificity of treatment and perhaps reducing drug resistance. Their application in the area of cancer takes benefit from the pathophysiology of tumors such as inadequate lymphatic drainage, greater penetrability, and retention effect along with the microenvironment.

Nanoparticles for Cancer Treatment

Nanoparticles are a promising means in diagnostics, treatment and medical imaging. They act as a target delivery tool and help in the delivery through two different methods, passive and active targeting. Active targeting employs antibodies, receptors, and peptides to identify tumor antigens as a means to offer target delivery. Passive targeting employs the improved penetrability and retention (EPR) effect seen in tumor vasculature as a means to assist cancer treatment. With the utilization of nanoparticles in the treatment of cancer, selectivity is enhanced and accidental systemic injury is strongly prevented. Nanoparticles not only take benefit of the improved permeability of tumors but also take advantage of the decreased lymphatic clearance of tumorous tissue compared to healthy tissue. This absence of clearance permits for the withholding of the nanoparticle and the drug it carries to stay in the tumors for an extended period of time, permitting for progressive therapeutic efficacy.

In addition, as an imaging tool, nanoparticles provide an enhancement in the sensitivity and specificity of diagnostic imaging, presenting a non-invasive and precise technique. Nanotechnology-based imaging probes are intended to identify a biomarker located on the cell surface of interest. The nanoparticles are supportive in refining the difference between cancerous and non-cancerous tis-

Table 1: Risk aspects in GC

Risk Aspects Related to the Progress of Gastric Cancer			
Risk factor	Observation	Risk Ratio (RR)	
Helicobacter pylori	Most vital modifiable risk factor	2.5%– 3%	
Smoking	Linked with increased risk of disease reappearance. The intensity of GC is almost doubled in smokers.	1.5%	
Alcohol	RR~1 in light/moderate drinkers and higher with heavy consumption.	~1% or higher	
Dietary salt and food preservation	Salt-based preservatives and lack of refrigeration results in an increased risk	~1% with each gram of salt consumed/day	
Fruit and vegetables	Reduced consumption leads to increased risk	~0.5%	
Pernicious anemia	People with anemia (a smaller number of RBCs) have a greater risk of GC.	6.8%	
Obesity	Being overweight or obese is a possible cause of cancers of the cardia.	The strength of this link is not yet clear.	
Genetics	Hereditary diffuse GC -produced due to alteration in the E-cadherin gene. 67% cumulative GC risk. Increased colon and lobular breast cancer risk. Lynch syndrome -defective DNA mismatch repair (MLH1 or MSH2 mutation). Increased risk of GC and colon cancer.	67%	

Table 2: The Mortality rate of GC

Worldwide prevalence of the most important types of gastrointestinal malignancies and related mortality rate						
Category	Esophageal	Gastric	Liver	Pancreas	Gall Bladder	Colon
Worldwide occurrence among all cancers (%)	3.8%	7.8%	7.9%	2.2%	1.1%	9.8%
Mortality	5.4% of cancer deaths globally	9.7%	9.2% 5-year survival rate in the USA	3.5%	1.4%	8.1%
Key Points	6 th highest cancer mortality	2 nd highest cancer mortality	3 rd highest cancer mortality	Lowest 5 year survival among GI cancers	-	Higher frequency in USA & EUROPE (13.3%)

sue. (See Figure 5), (Fang *et al.*, 2011). The method adopted is a unique type of fluorescent nanoparticles identified as Quantum Dots (QDs) have acquired momentum as an approach to enhance the imaging signal. QDs release photons of light of numerous wavelengths upon excitation. The benefit of those nanoparticles in diagnostic imaging over the conventionally used contrast agents is their low cost of synthesis and easy application. Additionally, current discovery is the application of nanoparticles in an MRI. It is well furnished that superparamagnetic iron oxide nanoparticles with lymphotropic qualities have been confirmed to efficaciously intensify the finding of tumors above 5 mm when compared to unenhanced MRI or computed tomography. Application of iron/iron oxide core/shell nanoparticles have extraordinary magnetic properties and may identify small tumors.

Outline of Gastrointestinal Therapy Developments in Gastric Cancer

Nanomedicine has demonstrated to have utility and potential use for GC treatment and diagnosis. The application of fluorescent magnetic nanoparticles is a clear illustration of the applicability of nanoparticles in GC. In contrast to traditional fluorescent dyes, fluorescent nanoparticles (FNPs) use tumor vasculature's EPR (enhanced permeability and retention) phenomenon to its advantage to stay inside tumor tissue, making FNPs an attractive choice for in vivo tumor imaging. Moreover, FNPs' large surface area and core-shell structure permit the manufacture of multimodal nanoparticles (MMNPs). MMNPs are derived by combining optical imaging modalities with nonoptical based imaging modalities. Such probes can further be packed with therapeutic cancer drugs together with the cancer-targeting agent. Recent advances have revealed that the overexpression of cyclooxygenase 2 (COX-2) elevates the lymphangiogenesis of tumors by elevating the expression of VEGF. COX-2 has been the target of several remedies in GC treatment.

Consequently, inhibition of COX-2 holds the ability as a possibly effective target of chemotherapy. The use of Ursolic Acid (UA), an inhibitor of COX-2, as a chemotherapeutic agent, has been known for some time. However, the hydrophobicity of UA makes it exhibit low bio availability and poor pharmacokinetics in vivo.

Moreover, it possesses a lack of specificity for cancer cells and causes toxicity to other tissues. To solve this matter, a UA-loaded nanoparticle was designed by Nano-precipitation utilizing amphiphilic methoxy poly (ethylene glycol)-polycaprolactone (MPEG-PCL) block copolymers

as UA carriers. Through an MTT assay and DAPI staining, UA-NPs were discovered to efficiently cause more death of cells by a greater inhibition of COX-2, caspase 3 activations, and greater cytotoxicity than UA alone. Such investigations recommend UA as a promising delivery system of UA in GC treatment (Zhang *et al.*, 2013).

The use of fluorescent nanoparticles (FNPs) for diagnosis purposes and cancer treatment has confirmed to be promising. This was established by a study in which a monoclonal antibody was combined with fluorescent magnetic nanoparticle for in vivo GC imaging. The antibody of choice was BRCA1 (Breast cancer-associated antigen 1 gene) as a consequence of finding the over-expression of BRCA1 protein in 64% of gastric cancerous tissues. The conjugated FNPs showed very low toxicity and were able to target in vivo GC cells. Therefore, the outcomes advise that it might have great potential in further imaging applications for diagnosis.

Diagnosis and Treatment of human gastric cell line MGC803 have been studied by means of RNase-conjugated quantum dot coupled to HER2 monoclonal antibodies (HER2-RQDs). Fluorescent imaging of tissues after administration of HER2-RQDs exhibited acceptance into gastric tissues with a non-appearance of signal in other tissues, suggesting selective gastric tissue uptake. Increased uptake by gastric tissue permitted the RNase A to be released into gastric cells and interfere with mRNA translation and protein synthesis, efficiently inhibiting cancer cells selectively (Ruan *et al.*, 2012).

Small interfering RNA (siRNA) facilitates the cleavage of target mRNA molecules that results in gene silencing at very specific sites. So, their application induces the silencing of cancer genes that have been identified to be related to the progress of cancer. Such genes comprise those accountable for proliferative oncogenes and inhibition of apoptosis. Their use in the field of nanotechnology was established in a study where liposomal nanoparticles were used in GC as treatment. These nanoparticles are bilayer membrane structures, made of phospholipids that have the ability to encapsulate hydrophilic agents such as therapy drugs and small interfering RNA (siRNA). The latter opens the opportunity for gene therapy in the field of cancer. Moreover, during a study done in the last year, CD44 isoforms such as CD44v6 were preferred as target genes for the inhibition and finding of metastatic GC cells. The target gene was then effectively downregulated and quietened through the application of Iron oxide superparamagnetic nanoparticles (PEG-g-PEI-SPION) as a delivery technique of siRNA.

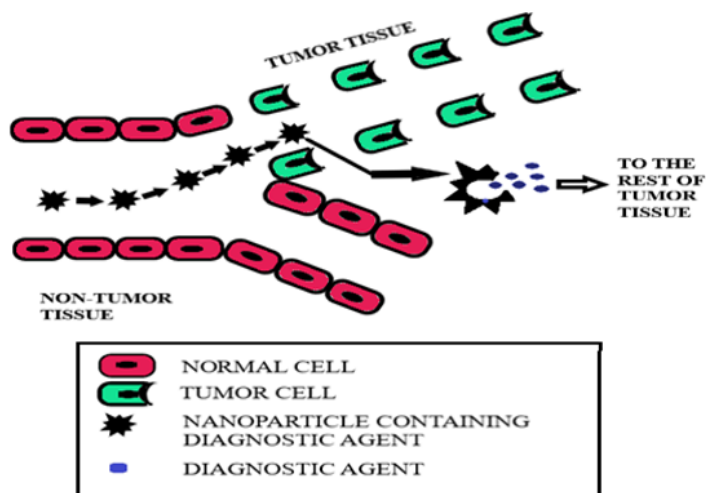


Figure 5: Diagram representing greater vascular permeability of tumor cells being employed for the delivery of treatment/diagnostic agents enclosed in a nanoparticle

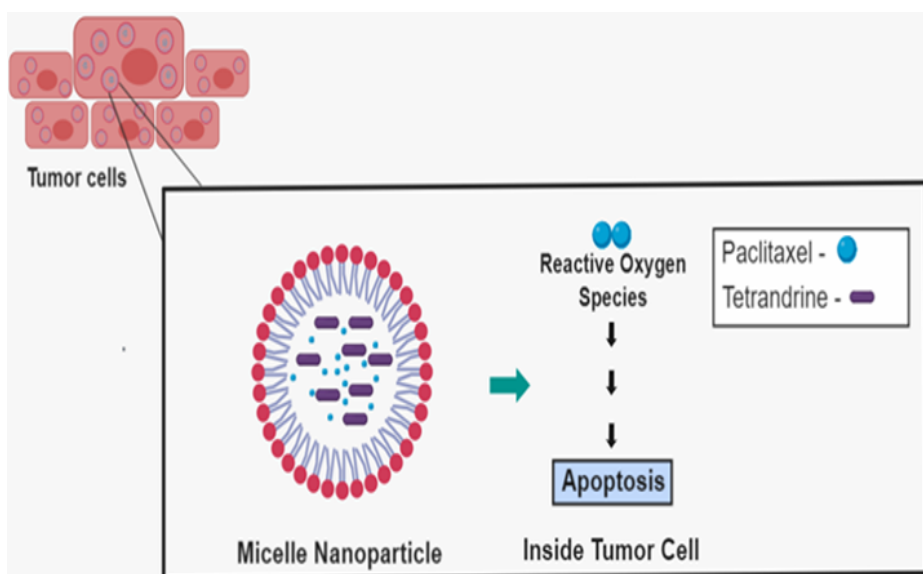


Figure 6: Illustration of targeted micelle nanoparticles loaded with both paclitaxel and tetrandrine, eventually bringing the apoptosis of cancer cells

These nanoparticles were preferred for their MRI visibility and transfection efficiency. This study renders PEG-PEFI-SPION a probable and efficient non-viral vector for cancer gene therapy (Chen *et al.*, 2013).

Finally, additional treatment of GC takes the benefit of the carrier properties nanoparticles to have. This is shown by the study done by Li *et al.* in the co-loading of Paclitaxel/tetrandrine nanoparticles as a therapy for GC. During this research, it was detected that the resistance ability of cancer cells to Paclitaxel treatment was overwhelmed by co-administration of Tetrandrine (Tet). The part of Tet in this therapy was to bring production of reactive oxygen species which overwhelmed intracellular antioxidant capac-

ity and permitted for an intensification of Paclitaxel potential against the tumorous cells as seen in Figure 6, (Li *et al.*, 2012). This entire procedure was named oxidation treatment.

Key Points

Nanoparticles provide the opportunity of an enhanced and earlier diagnosis of cancer, permitting the localized therapy of neoplasms and tumor cells, reducing the potential side effects that occur with the presently used therapies. They provide the potential for enhanced multidrug-resistant therapy of multidrug-resistant cancers.

The smaller size of nanoparticles also rises their solubility in the bloodstream and their ability to spread into tissue with smaller pore sizes, providing them an extensive range of accessibility and tissue pene-

Table 3: Information on nanoparticle technology therapies for gastric cancer

Category	Treatment	Key points
Gastric cancer	<ol style="list-style-type: none"> 1. Fluorescent nanoparticle imaging 2. PEG-PEI liposomes 3. Ursolic acid nanoparticle to suppress overexpressed COX-2 4. Nanoparticles coloaded with paclitaxel and tetrandrine 	<ol style="list-style-type: none"> 1. Coupled to antibodies for highly expressed receptors 2. Target chemo and siRNA therapy 3. Increases bioavailability and effectiveness of ursolic acid 4. Tetrandrine induced ROS formation increases paclitaxel efficiency

tration.

A significant part of gastrointestinal cancers are not responsive to the recent chemotherapeutic and radiotherapeutic agents; additional advancement of nanoparticle approaches demonstrates a promising tool in their potential efficacy. (See Table 3), (Vyas *et al.*, 2014).

Limitations and Challenges of Nanotechnology

The high cost of development which would prevent extensive access to the advantages of the technology, even in primary stages. The usage of nanoparticles may be restricted by the science of cancer cells in their frequency of efficiency. If a particular molecular target has developed resistance to treatment, nanoparticles can assist to solve this by permitting more intracellular accumulation of the therapeutic agent, and limited uptake by healthy tissues, thus overcoming the resistance (Vyas *et al.*, 2014).

Role of Monoclonal Antibodies for Gastric Cancer Treatment

Even though several therapies are now available for GC, the 3-year and 5-year OS (overall survival) rates are still less than 35% and 25% correspondingly. The symptoms are nonspecific during the initial phases of GC. More specific symptoms, for example, weight loss and anemia, are observed in progressive stages. But effective treatment choices are limited in advanced phases and the average survival is 9–10 months. For years, therapy choices for cancer have been chemotherapy and radiation with great chances of tumor degeneration resulting from drug resistance. All this information highlights the requirement for further novel and efficient anti-cancer treatments. One of the recent approaches in advanced cancer therapy is Immunotherapy. Together with the growing number of clinical studies and investigation of biomarkers and clinical data, a desirable role of immunotherapy in GC is evolving. Intracellular and extracellular pathways accountable for cell proliferation, apoptosis and angiogenesis could be suitable targets for cancer immunotherapy. The earliest observation of using immunother-

apy in cancer goes back to 1891 when William B Coley injected the streptococcal microorganism into cancer patients and detected shrinkage of the cancer cells.

Overexpression of VEGF (Vascular endothelial growth factor) and its receptor (VEGFR) (Vascular endothelial growth factor receptor) was observed in 40% of GC case reports and was connected with the progressive phase of cancer and poor diagnosis. By means of a VEGFR-2 monoclonal antibody (mAb) such as ramucirumab progresses survival in GC. Overexpression of human EGF receptor 2 (Her2) was also observed in advanced GC, and anti-Her2 mAbs like trastuzumab presented survival benefits in those patients.

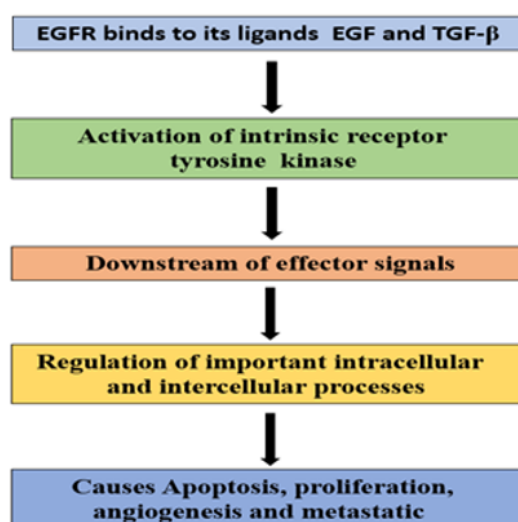


Figure 7: Flow chart illustrating the action of EGFR

The capability of an immune system to identify and terminate non-self-cells (such as cancer cells) before they can cause harm, is known as immune surveillance. Scientific usage of tumor immunotherapy is supporting the immune system towards more potentiated passive or active immune responses against cancer. Usage of mAbs as monotherapy or

Table 4: Clinical Studies data of Trastuzumab in Gastric cancer

Detailed information on Clinical studies of Trastuzumab in Gastric Cancer							
Author (year)	Study name/phase	Monoclonal antibody	Mechanism	Regimen	Results	Safety Profile	
Sawaki et al. (2012)	ToGA	Trastuzumab	Inhibition of Her2	Trastuzumab+ chemotherapy (G1) versus chemotherapy alone (G2)	MOS: 15.9 months in G1 and 17.7 months in G2	All grade SD: 51% G1 & 50% G2 Grade \geq 3 SD: 43% G1 & 36% G2	
Thuss-Patience et al. (2017)	GATSBY (Phase II/III)	Trastuzumab	Inhibition of Her2	Trastuzumab versus docetaxel	MOS: 7.9 months with trastuzumab emtansine given at 2.4 mg/kg weekly and 8.6 months with taxane	In general, the rate of SDs was lower in the trastuzumab group versus taxan group	

MOS: Median overall survival; MRD: Median remission duration; RR: Response rate; SD: Standard deviation; DCR: Disease control rate

adjuvant therapy is growing in various categories of cancer to attain survival benefits and more prominent treatment. Hybridoma technology developed by Kohlen and Milstein surfaced the technique for mAbs productions and made preliminary significant changes in clinical oncology. These days, new modalities, which have significant benefits due to their small sizes, such as specific tumor targeting, high affinity, and low immunogenicity, have been established. Cancer immunotherapy utilizing tumor antigen (Ag)-specific mAbs, which makes tumor Ags available to the destructive effects of the immune system. Abs exercise their anti-tumor properties through mechanisms like Agglutination, Neutralizing signaling proteins and Occupying ligand-binding sites on receptors. An example of the latter is inhibition of growth factor ligand-receptor binding with subsequent inhibition of tumor cell growth. Trastuzumab is a mAb that exhibits by this mechanism in breast cancer. Additionally, mAbs have milder side effects (allergic side effects) compared with cytotoxic drugs used in chemotherapy.

The latest approaches under research in tumor therapy consist of Epidermal GC receptor (EGFR) inhibitors, Anti-angiogenesis agents, Apoptosis promoters and Specific immunotherapies.

Anti-Her2 mAb

Her2 is a tyrosine-kinase receptor associated with regulation of proliferation, differentiation, and apoptosis. The expression of Her2 in cancer cells is greater than noncancer cells. Overexpression

of Her-2 is connected with tumor development and aggressiveness (tumor size, invasion, and metastasis), and has negative properties on overall survival (OS), making it a significant prognostic marker. Her2 overexpression was observed in breast, ovarian, lung, prostate cancers and it was first stated in GC by Saki et al. and Fukushima et al. in 1986. The intermediate proportion of Her2 overexpression in gastroesophageal junction (GEJ) adenocarcinoma found to be 22%. In the systematic analysis, Jorgensen et al. determined that patients with Her2+GC exhibit significant higher stages of cancer and poor survival.

Trastuzumab

(Herceptin) is a mAb that targets Her2 acting by several approaches like Inhibition of Her2 dimerization, Inducing receptor destruction and Antibody-associated cytotoxicity. It was the earliest molecular-targeted therapy that resulted in survival benefits in advanced gastric and oesophageal cancer. Inhibitory actions of trastuzumab were first witnessed on human GC cell lines in invitro outcomes, and it presented synergistic antineoplastic action together with chemotherapy in vivo studies ([Sawaki et al., 2012](#)). The toxic effect of trastuzumab is Cardiotoxicity. This dose-independent side effect is generally reversible after the termination of Trastuzumab. Refer Table 4 for detailed information on Clinical studies of Trastuzumab in Gastric Cancer ([Sawaki et al., 2012](#); [Thuss-Patience et al., 2017](#)).

Table 5: Clinical studies of Anti-EGFR Monoclonal Antibodies in Gastric Cancer

Detailed information on clinical studies of Anti-EGFR Monoclonal Antibodies in Gastric Cancer.						
Author (year)	Study name/phase	Monoclonal antibody	Mechanism	Regimens	Results	Safety profile
Lordick et al. (2013)	EXPAND (Phase III)	Cetuximab	Inhibition of EGFR	Cetuximab+ chemotherapy(G1) Chemotherapy alone(G2)	Median PFS: 4-4 months G1 vs. 5.6 months G2	Any grade of serious SDs: 54% G1 vs. 44% G2 Grade 3-4 SDs: 83% G1 vs. 77% G2
Waddell et al. (2013)	REAL3 (Phase III)	Panitumumab	Inhibition of EGFR	Panitumumab+ modified-dose chemotherapy(G) Chemotherapy alone(G2)	Median OS: 8.8 months G1 vs. 11.3 months G2	The incidence of grade 3-4 of non-hematologic SDs & lower rate of hematologic SDs was observed in G1
Trarbach et al. (2013)	Phase I	Matuzumab	Inhibition of EGFR	Matuzumab+ chemotherapy	ORR: 26.7% (modest anti-tumor activity)	Acceptable safety

MOS: Median overall survival; MRD: Median remission duration; PFS: Progression-free survival; SD: Side effect; DCR: Disease control rate

Anti EGFR mAbs

EGFR (Epithelial growth factor receptor) is an additional type of tyrosine kinase growth factor receptor superfamily and is a potential target in cancer immunotherapy. Expression of EGFR occurs in various tissues like skin, gut, kidney and leads to tumor growth and invasion. EGFR overexpression was stated in 27–64% of GC cases and EGFR inhibition might be a potentially ideal target for GC treatment. Refer Figure 7 for the Flow chart illustrating the action of EGFR.

Two categories of EGFR inhibitors studied in GC involved,

1. Oral Tyrosine Kinase Inhibitors Gefitinib and Erlotinib
2. mAbs: - Cetuximab, Panitumumab, and Matazumab

Cetuximab

It is an anti-EGFR mAb, binding to EGFR and diminishes ligand-receptor interaction. Satisfactory outcomes of preclinical and Phase II clinical trial studies proposed that cetuximab has efficient survival benefits, safe and efficient therapeutic actions in advanced gastroesophageal cancer, mainly when used together with chemotherapy.

Panitumumab

Panitumumab is an entirely humanized anti-EGFR mAb that can increase the survival rate in advanced colorectal cancer. In Phase III, clinical studies have shown by Weddelletal *et al.*, the combinational regimen of oxaliplatin, capecitabine, and epirubicin without or with panitumumab were verified on 522 patients suffering from gastroesophageal adenocarcinoma. They stated that there was no increase in OS with a combination of panitumumab and EOG regimen ([Waddell et al., 2013](#)).

Table 6: Clinical studies of Anti-VEGF Monoclonal Antibodies in Gastric Cancer

Detailed information on clinical studies of Anti-VEGF Monoclonal Antibodies in Gastric Cancer					
Study name/phase	Monoclonal antibody	Regimen	Results	Safety profile	Ref
REGARD (Phase 3)	Ramucirumab	Ramucirumab monotherapy with 8 mg/kg, intravenously once every two weeks or placebo	Median OS: 5.2 months with Ramucirumab vs. 3.8 months with placebo	A similar rate of SDs except for Higher hypertension rate in the ramucirumab arm	Fuchs et al. (2014)
Phase 2	Bevacizumab	B-DOCT: Trastuzumab+ bevacizumab + docetaxel, oxaliplatin + capecitabine	Median PFS: 10.8 months OS: 17.9 months 1-year OS: 79% 1-year PFS: 52% ORR: 74%	Safe and tolerable	Meulendijks et al. (2016)

Matuzumab

Matuzumab is another entirely humanized anti-EGFR mAb. Trackback *et al.*, showing Phase I clinical studies to explore matuzumab plus 5-fluorouracil, leucovorin, and cisplatin. The study confirmed the satisfactory safety profile of this treatment in advanced gastric and gastroesophageal adenocarcinoma patients with intermediate anti-cancer action ([Trarbach et al., 2013](#)). Refer Table 5 for detailed information on clinical studies of Anti-EGFR Monoclonal Antibodies in Gastric Cancer ([Waddell et al., 2013](#); [Lordick et al., 2013](#)).

Anti-VEGF mAb

Senger *et al.* first presented VEGF (Vascular endothelial growth factor) as a vascular permeability factor. It is identified as a significant agent in physiological and pathological angiogenesis. Angiogenesis has vital roles in cancer growth. Over-expression of VEGF and VEGFR was observed in 36–40% of GC patients. Studies have revealed that greater serum VEGF levels potentially connected with inadequate prognosis in GC patients. Therefore, in vivo studies displayed antitumoral actions of anti-VEGFR treatment, possibly facilitated by decreasing tumor vasculature and elevated endothelial cell apoptosis. Using VEGF-A and VEGFR2 (Vascular endothelial growth factor receptor 2) inhibitors might be an alternative approach in cancer treatment to decrease metastasis and tumor vessel supply.

Ramucirumab

In Phase III REGARD clinical studies, the ramu-

cirumab monotherapy was observed on 355 formerly treated GEJ adenocarcinoma or advanced gastric patients belonging to 29 countries. Patients separated into 2 categories: Placebo group and ramucirumab group (8 mg/kg given through I.V route once every two weeks). The outcomes of this clinical study recommended that ramucirumab has survival benefits as monotherapy in earlier treated advanced gastric or GEJ adenocarcinoma patients ([Fuchs et al., 2014](#)).

Bevacizumab

Bevacizumab is one more anti-VEGF mAb used in malignancies like non-small-cell lung cancer (NSCLC), breast, colorectal and ovarian. This mAb prevents the association between VEGF-A and its receptors VEGFR1 and VEGFR2. Phase I clinical trial recommended efficient advantages in GC. In a single-arm Phase II clinical trial by Didier Meulendijks *et al.*, combination therapy was employed in 3-weekly cycles for six cycles in 25 HER2 + GC patients. The regimen involved bevacizumab, trastuzumab, docetaxel, oxaliplatin, and capecitabine (B-DOCT). The outcomes were efficient and two patients were free of disease 2 years after therapy. This combination therapy is safe and tolerable ([Meulendijks et al., 2016](#)). Refer Table 6 for detailed information on clinical studies of Anti-VEGF Monoclonal Antibodies in GC.

Robotic Surgery for Gastric Cancer

Development of Robotic-assisted surgery was performed for use in general and paediatric surgery, gynaecology, and urology. Surgical robotic systems

Table 7: Patents Obtained in the field of Nanotechnology

S. NO	Document	Document Title	Claim
1	US20190032050A1 United States	RNA nanoparticle for treatment of GC	An artificial RNA nanostructure molecule, comprising: a multiple branched RNA junction motifs comprising at least one RNA oligonucleotides, and a GC-targeting module coupled to the RNA junction motif.
2	US20180369422A1 United States	Nanoparticles for cancer detection	A method of detecting a cancer cell or tumor in a subject by administering into the peritoneum, a nanoparticle that comprises a detectable agent and detecting said nanoparticle at the site of a cancer cell or tumor, thereby detecting the cancer cell or tumor.
3	US20160213711A1 United States	Cancer Therapy with Silver Nanoparticles	A method of inhibiting the growth or proliferation of a cancer cell comprising contacting the cancer cell with an effective amount of silver nanoparticles
4	US20160151298A1 United States	Docetaxel polymeric nanoparticles	A method of treating a solid tumor cancer inpatient by intravenously administering the patient an effective amount of therapeutic nanoparticle suspension comprising docetaxel, a surfactant, and an aqueous suspending medium
5	US20190022246A1 United States	Silicon nanoparticle with platinum anti-cancer agent	A silica nanoparticle comprising a platinum anti-cancer agent, wherein the platinum anti-cancer agent is conjugated to silica directly, through an oxygen linker, or a nitrogen linker
6	US20170020816A1 United States	Targeted polymerized nanoparticles for cancer treatment	A hybrid polymerized liposomal nanoparticle, comprising: a polymerizable lipid with at least one PEGylated polymerizable lipid having a PEG polymer chain; and a non-polymerizable lipid
7	US20190076457A1 United States	Nanoparticle to target cancer	A pharmaceutical salt comprising polyethylene glycol-block-poly(L-lysine) polymer moiety, a cholecystokinin-B (CCK-B) receptor-ligand and a siRNA complexed with the poly(L-lysine) of the polymer moiety.
8	US8242165B2 United States	Mucoadhesive nanoparticles for cancer treatment	Treating cancer by a plurality of nanoparticle comprising glyceryl monooleate fatty acid ester core and surface layer, placing chitosan on the surface layer to create a positive charge to make each nanoparticle more mucoadhesive to negatively charged mucin of cancer cell and incorporating cancer therapeutic agents into the core

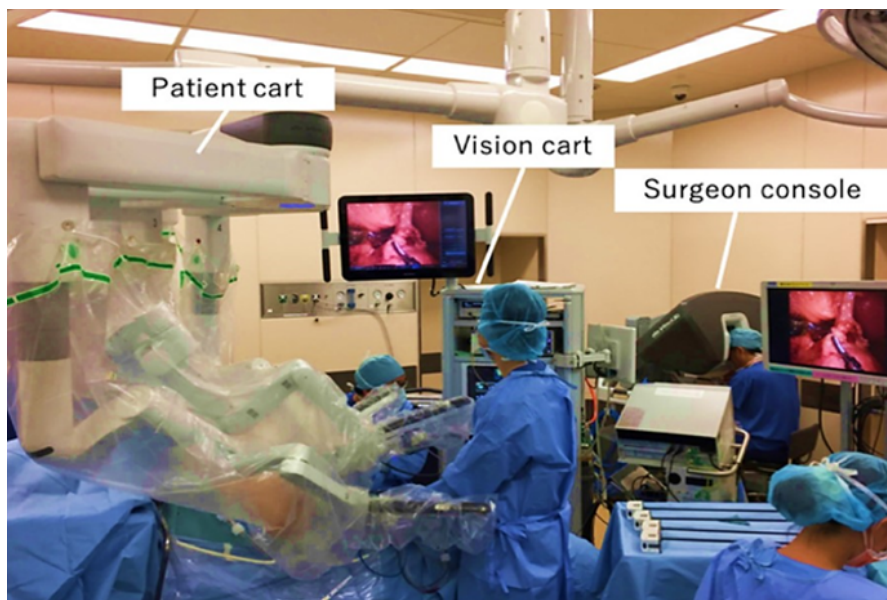


Figure 8: Layout of the Da Vinci Surgical System comprises the patient cart, vision cart, and surgeon console

have been presented into the area of GC therapy as an enhanced technology that has overwhelmed the technical limits of laparoscopy. Since 2005, a robotic system has been employed for GC surgery in Korea, and several skilled MIS specialists have stated that in comparison with laparoscopic gastrectomy, robotic gastrectomy is safe and effective. In comparison with laparoscopic surgery, robotic surgery usage for GC suggestively reduces intraoperative blood loss. After robotic gastrectomy, the duration of stay in the hospital is short compared to an open surgical operation. But the time period required for an operation involving robotic gastrectomy was lengthier. Some researchers have recommended that the possibility and benefits of robotic surgery to deal technically-challenging difficult case aspects (for example, very advanced cancer, multiorgan resection, and function preserving surgeries) should be examined. Advantages of Robotic surgery inpatient care includes Multi-articulated movement, reduced hand tremor, the stable and firm camera platform, and much accurate, specific dissections. Disadvantages include nonappearance of tactile feeling and expensive.

Song *et al.* conveyed their understanding of 100 patients suffering from early GC who undertook robot-assisted gastrectomy (33 total and 67 subtotals, with D1 lymphadenectomy) using the da Vinci system. The average operative time, length of stay and lymph node yield were 231 minutes, 7.8 days and 36.7, respectively. There were no deaths. Even though other studies reveal assessing the safety of robotic gastrectomies has been carried out, but additional multi-center, potential, and relative trials

are necessary. Figure 8 illustrates the Layout of the Da Vinci Surgical System comprises the patient cart, vision cart and surgeon console (Coratti *et al.*, 2013).

Table 7 is regarding the Patents obtained in the field of Nanotechnology that explains about the various applications of Nanoparticles for the diagnosis and therapy of cancers (Cui *et al.*, 2015).

CONCLUSIONS

GC is a malignant disease with a generally deprived long-term prognosis. The majority of GCs are sporadic subtypes that are strongly associated with environmental risk factors. In the last few decades, various mechanisms of GC genesis have been elucidated, which has resulted in primary and secondary prevention, such as healthy lifestyle and H. pylori eradication. Consequently, the incidence of GC has started to decline. Every patient with GC needs to be treated according to the individual plan made by MDT. Recent advances in molecular targeting to improve on this outcome led to the development of trastuzumab as a new standard of care for HER2-positive patients with GC. But as only about 20% of the patients with GC are HER2 positive, this therapy addresses their needs effectively but not others. Similarly, ramucirumab is able to control the disease and improve outcomes in patients with VEGFR2-positive GC. Further work needs to develop more effective and specific therapies that hopefully have fewer adverse events compared with the currently available therapeutic regimens. Nanoparticles offer the possibility of improved and earlier diagnosis of cancer. In addition, their characteristics allow for

the localized treatment of neoplasms and cancer cells, decreasing the potential side effects that come with the currently used treatments. They can also encapsulate drugs and prevent them from having a toxic effect on healthy tissue during their transit to their sites of action. In the utilization of nanoparticles in the field of cancer, it will be important to consider the cost to patients. Although the promising effectiveness of nanoparticles is overwhelming, the question of whether this would be affordable to patients is still unclear. Advancement has been made in understanding the pathogenesis and the molecular biology of GC and in optimizing the available treatment options and modalities. However, in the future, the focus should be on further unraveling the taxonomy of GC, fine-tuning treatment strategies, and developing new drugs for patients with advanced GC.

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