



Overview of Gastric Cancer Treatment and Recent Developments – An Updated Review

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ABSTRACT

Gastric Cancer (GC) is one among 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 an inoperable disease at diagnosis or have recurrent disease after resection with curative intent. Surgery remains the principle therapy, while perioperative and adjuvant chemotherapy and chemoradiation can improve the outcome of GC therapy. Targeted therapies such as Trastuzumab, an antibody against HER2 and the VEGFR-2 antibody ramucirumab highly preferred in GC. Since the last few years, immunotherapy became a significant approach for the cure of various cancers like GC. In the present review, we have put forward the various stages of GC and all the possible advanced treatments for GC. Surgery is still the first choice analysed in GC followed by chemotherapy and radiotherapy. New frontiers in treatment suggest the growing consideration for intraperitoneal administration of chemotherapeutics and a combination of traditional drugs with the newer generation. A note is added to relevant studies dealing with neoadjuvant and adjuvant treatment concepts and gives an overview of latest trends and developments in GC treatment.



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INTRODUCTION

Gastric Cancer (GC) is one among the serious diseases prevailing globally. GC is an immense global life-threatening health issue, which takes 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. The highest rates are noticed in Eastern Europe, Central Europe, and East Asia accounting together for 87% of the world's new GC cases. Remarkable lower rates are observed in North America and Africa. Graphically representation in Figure 1 estimates incidence (cases in both genders) of gastric cancer worldwide in the year 2012 ([Globacan Graph production, 2012](#)).

The chances of recovery from the ailment depend on the stage at which has been noticed and complete surgical resection is regarded as the only choice of cure. For tumors localized to the invasion of the mucosa or submucosal at diagnosis, 5-year survival rates are among 70% and 95% through exclusive management of surgery. Advancement stage

Estimated incidence (cases in both sexes) worldwide in 2012

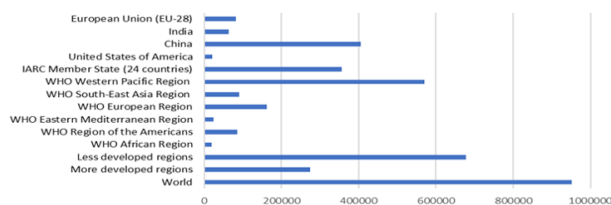


Figure 1: Stomach Cancer Fact Sheet.

in GC is diagnosed through multimodality treatment options such as surgery, chemotherapy, radiation therapy, chemoradiation, targeted therapy, and immunotherapy. The high death rate related to GC is typically attributed to the deficiency of informative tumor markers for primary detection in addition to efficient medical treatment for patients in progressive stages of the disease. Initial detection is advantageous and critical for successful surgical eradication of GCs because peritoneal propagation and local and distal metastases frequently appear in the late stages of GC and significantly diminish the efficiency of surgery. In spite of significant developments in the treatment of GC and declining tendencies in prevalence and death rates, several patients yet die because of cancer development, reappearance, as well as metastasis.

For various phases of gastric cancer, Surgery is would be a part of the treatment approach if it could be performed. For patients who are in GC stage 0, 1, 2, or 3 and those who are with a proper health condition to bear the surgical operation, surgery (often together with further treatment options) provides the genuine opportunity for curing in such a situation. Surgery is usually performed to eliminate the gastric tumor and the portion or whole of the stomach together with few closely located lymph nodes.

On the other hand, Chemotherapy can be provided a fundamental and sometimes as the main therapy for GC which would expand (metastasized) to organs at a distant location. This helps to diminish the symptoms of a few patients and promotes their life span by causing shrinkage of cancerous cells or slowing down their growth. As an outcome, the rapid developments in the area of tumor biology considerations are concentrated on the newer methods of molecular targeted therapy for advanced GC. Molecular targeted inhibitors efficiently control increased levels of molecules in cancer cells and the signalling pathways that are closely related to tumorigenesis, thus controlling the biological behaviour of cancer cells. Molecular targeted therapy not only progresses the selectivity and specificity of anti-cancer therapy but also avoids non-selective toxicity and

resistance (Riquelme *et al.*, 2015).

Immunotherapy is also one of the new modalities in advanced cancer therapy. Along with the growing count of clinical studies and analysis of biomarkers and clinical data, a promising role of immunotherapy in GC is emerging. Intracellular and extracellular pathways responsible for cell proliferation, apoptosis and angiogenesis could be appropriate targets for cancer immunotherapy. In this review, an effort is put to discuss the treatment options overview and their utilization in different stages of gastric cancer.

STAGES OF GASTRIC CANCER

The below-mentioned stages are described for GC (Hubbard *et al.*, 1986),

1. Stage - 0 (Carcinoma in Situ)
2. Stage - I
3. Stage - II
4. Stage - III
5. Stage - IV

The stomach is part of the digestive system, that is extending from the mouth to the anus. It is a J-shaped muscular organ in the superior portion of the abdominal region. It is linked to the Oesophagus and Small intestine. The stomach wall has many layers that include the mucosa layer (mucous membrane) which is the inner lining of the stomach. The following layer covering the mucosa is the submucosa which comprises connective tissue that holds lymph vessels and larger blood vessels, nerve cells, and fibres. The muscularis propria (or muscularis externa) is the subsequent layer covering the submucosa. The serosa (visceral peritoneum) is the fibrous membrane covering the exterior stomach portion. Figure 2 describes the layers of the stomach wall (Hubbard *et al.*, 1986). A cancerous tumor of the stomach can invade, or grow into, and usually destroys the neighbouring tissue. It could also spread, or metastasize, to other areas of the human body. Stomach cancer generally starts in the inner linings of the stomach wall (called the mucosa). Upon growing, it conquers deep into the stomach wall and later invades the stomach wall. If the tumor attacks only the mucosa or submucosa (the layer of the stomach wall below the mucosa), it is known as early stomach cancer (See Table 1, Figure 3).

Symptoms of GC

Table 1: Stages of Gastric Cancer

S. No	Stages of Gastric Cancer		Description
1.	Stage 0 (Carcinoma in Situ)		Abnormal cells were seen in the mucosa, the innermost layer of the stomach wall which might develop into cancer, spreading into neighbouring normal tissues.
2.	Stage- I	Stage IA	Cancer is observed in the mucosa and might have propagated to the submucosa, the layer of tissue subsequent to the mucosa.
		Stage IB	1. Cancer is observed in the mucosa and might have propagated to the submucosa. Cancer may propagate to 1 or 2 adjacent lymph nodes; or 2. Cancer has developed in the mucosa and has propagated to the muscle layer.
3.	Stage- II	Stage IIA	1. Cancer might have propagated to the submucosa. It has spread to 3 to 6 adjacent lymph nodes; or 2. Cancer has propagated to the muscle layer of the stomach wall. Cancer has spread to 1 or 2 adjacent lymph nodes; or 3. Cancer has propagated to the subserosa, a layer of connective tissue subsequent to the muscle layer of the stomach wall.
		Stage IIB	1. Cancer might have propagated to the submucosa. Cancer has propagated to 7 to 15 adjacent lymph nodes; or 2. Cancer has propagated to the muscle layer. Cancer has propagated to about 3 to 6 adjacent lymph nodes; or 3. Cancer has propagated to the subserosa. Cancer has propagated to about 1 or 2 adjacent lymph nodes; or 4. Cancer has propagated to the serosa, the outermost layer
4.	Stage- III	Stage IIIA	1. Cancer has propagated to the muscle layer. Cancer has propagated to 7 to 15 adjacent lymph nodes; or to the subserosa. 2. Cancer has propagated to 3 to 6 adjacent lymph nodes; or to the serosa. Cancer has propagated to 1 to 6 adjacent lymph nodes; or 3. Cancer to adjacent organs like colon, spleen, diaphragm, liver, pancreases, adrenal gland, abdomen wall, small intestine, kidney or the back of the abdomen.
		Stage IIIB	1. Cancer might have propagated to the submucosa or to the muscle layer of the stomach wall. Cancer has propagated to 16 or more adjacent lymph nodes; or 2. Cancer has propagated to the submucosa or to the serosa. Cancer has propagated to 7 to 15 adjacent lymph nodes; or 3. Cancer has propagated from the stomach to neighbouring organs, such as colon, spleen, diaphragm, liver, abdomen wall, pancreas, kidney, adrenal gland, or to the back of the abdomen, or the small intestine. Cancer has propagated to 1 to 6 adjacent lymph nodes.
		Stage IIIC	1. Cancer has propagated to the subserosa or to the serosa. Cancer has propagated to 16 or more adjacent lymph nodes; or from the stomach into nearby organs, such as colon, spleen, diaphragm, liver, abdomen wall, pancreas, kidney, adrenal gland, or to the back of the abdomen or the small intestine. Cancer has propagated to 7 or more adjacent lymph nodes.
5.	Stage- IV		1. Cancer has propagated to other areas of the human body, such as the liver, lungs, distant lymph nodes, and the tissues lining the abdomen wall.

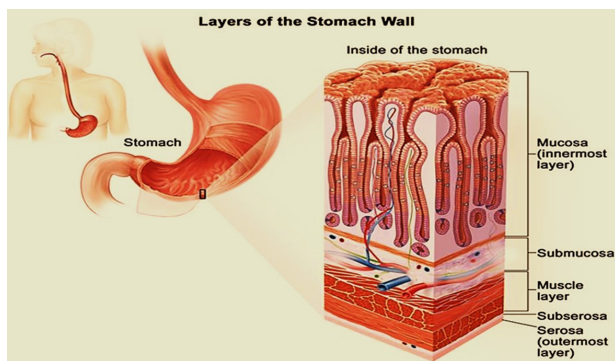


Figure 2: Layers of the stomach wall showing innermost layer mucosa; submucosa, the muscle layer, subserosa and serosa as the outermost layer.

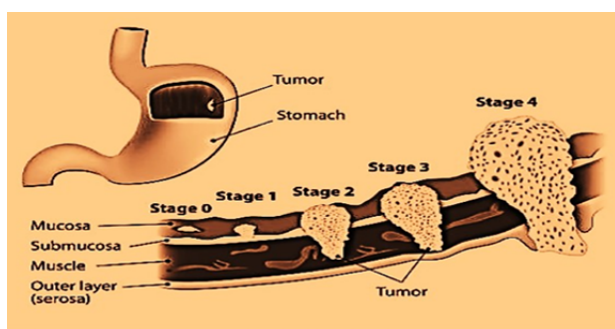


Figure 3: Stages of Stomach Cancer

Maximum patients suffering from gastric cancer in early-stages are asymptomatic. Thereof, medical diagnosing is occasionally done when an infection is at the progressive phase. The important and widely known symptoms during medical diagnosing include weight loss, dyspepsia, abdominal pain, and anorexia. Dysphagia may be exhibited by patients having tumors at the proximal stomach or gastro-oesophageal junction. The maximum symptoms of GC indicate the advanced stage disease. By the time period they progress, the disease is almost invariably too far advanced for curative procedures. Signs and symptoms of GC include Postprandial fullness, Dysphagia, Vomiting or Nausea, Hematemesis, Melena or pallor from anaemia, Loss of appetite, palpably enlarged stomach with succussion splash, enlarged lymph nodes like Irish node (anterior axillary) and Virchow nodes (left supraclavicular).

Late complications of GC might include,

1. Pathologic peritoneal and pleural effusions
2. Impediment of the gastric outlet, gastro-oesophageal junction, or small bowel
3. Haemorrhage in the stomach from oesophageal varices or at the anastomosis after surgery
4. Intrahepatic jaundice produced by hepatomegaly and Extrahepatic jaundice

5. Inanition from starvation or cachexia of tumor origin (Nagaich, 2018).

Treatment option overview

Six kinds of recognized treatments used for GC are,

1. Surgery
2. Chemotherapy
3. Chemoradiation
4. Immunotherapy
5. Targeted therapy
6. Radiation therapy

Surgery for stomach cancer

For various phases of gastric cancer, Surgery is would be a part of the treatment approach if it could be performed. Surgery is usually performed to eliminate the gastric tumor and the portion or whole of the stomach together with few closely located lymph nodes. During situations where the GC is too prevalent to be taken off entirely, surgery helps those diseased individuals by avoiding blood loss from tumors or by preventing the stomach from getting clogged by the growth of the tumor. This kind of surgery is termed as palliative surgery. It implies to lessen the progress of a disease and also to relieve unwanted symptoms for as long as possible, rather than trying to cure the disease (Hubbard et al., 1986). This kind of surgical procedure typically relies on which portion of the stomach the tumor growth is located and the intensity of cancerous tissue in neighbouring tissue. Various types of surgical procedures for treating Gastric cancer,

1. Endoscopic Resection
2. Subtotal (partial) Gastrectomy
3. Total Gastrectomy
4. Placement of a feeding tube
5. Lymph Node removal
6. Palliative Surgery for unresectable cancer

Endoscopic Resection

Endoscopic submucosal and mucosal resection are usually done only to cure few cancers present in very early-stages, in situations where the possibility to expand to lymph nodes is too little. These practices don't need an incision/cut in the skin. As an alternative, an endoscope, a flexible, elongated tube provided with a small video camera at its end is passed

through the throat region, into the stomach by the surgeon. It is also possible to pass surgical operating equipment through this endoscopic tube to discard the tumors and portion of the gastric wall surrounding it. Figure 4 illustrates the Endoscopic mucosal resection showing injection, circumferential marking, snare excision, and removal of early gastric cancer (Soetikno *et al.*, 2003).

Subtotal (partial) Gastrectomy

Cancer in the lower part of the stomach, then this procedure is usually considered. In certain circumstances operation is also done for those tumors only in the upper portion of the stomach. It involves either removal of the only portion of the stomach at one time together with some portion of the oesophagus or small intestinal initial portion i.e. the duodenum. The residual part of the stomach is then reconnected. The advantage of partial gastrectomy is the consumption of food becomes easy only if some portion of the stomach is removed instead of the whole organ (See Figure 5).

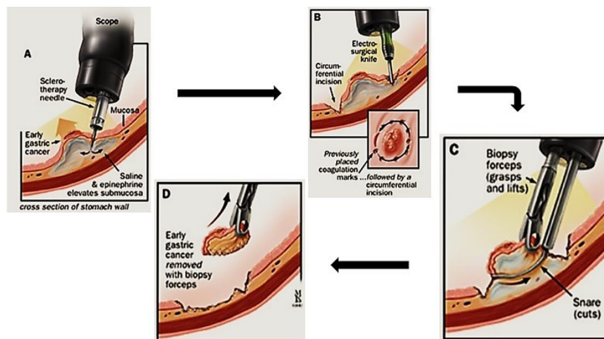


Figure 4: Endoscopic mucosal resection showing injection, circumferential marking, snare excision, and removal of early gastric cancer

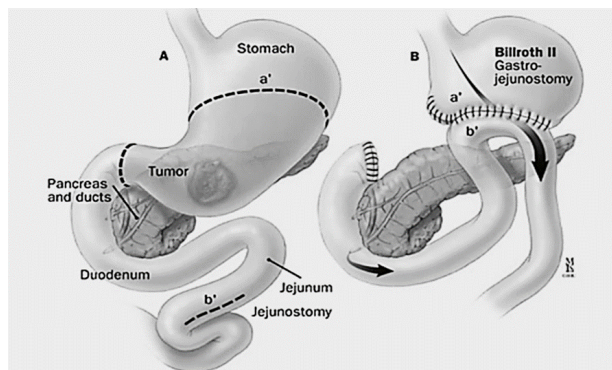


Figure 5: A- Low subtotal gastrectomy; B- Billroth II anastomosis

Total Gastrectomy

This Surgical procedure is performed for cancer if has been extended to the entire portion of the stomach. It is even recommended for cancers located

in the superior portion of the stomach, close to the oesophagus. The surgeon first discards the complete stomach, then neighbouring lymph nodes, omentum, and might discard the spleen along with some portions of intestines, pancreas, oesophagus, or few adjacent organ tissues. The terminal portion of the oesophagus is further linked to the portion of the small intestine allowing the consumed food to pass into the intestinal tract. The patients who undergo this kind of surgery usually consume food more frequently because their stomach had been discarded completely making them consume only a little quantity of food at a single point of time. The majority of Total and Subtotal gastrectomies are performed by means of a large incision in the abdominal skin (Huscher *et al.*, 2005) (See Figure 6).

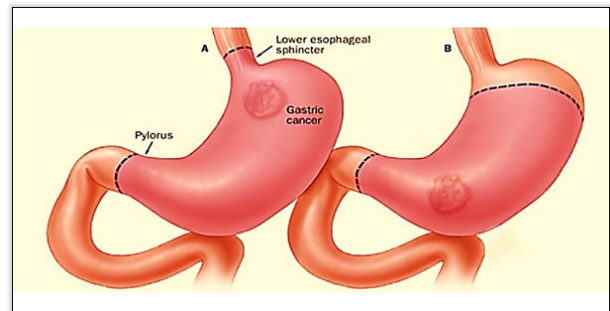


Figure 6: A- Total gastrectomy; B- subtotal gastrectomy

Placement of a feeding tube

Few individuals face a problem in taking adequate nourishment after surgical treatment for GC. In order to solve this, a flexible tube is introduced into the intestinal part during gastrectomy. The terminal portion of that tube, known as a J tube (jejunostomy tube), lies out of the abdominal skin. Thus, this approach helps in preventing and treating malnourishment, by passing liquid food right into the intestinal tract (See Figure 7).

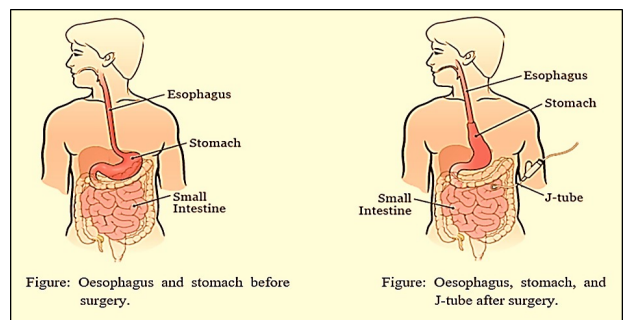


Figure 7: Placement of a feeding tube

Lymph node removal

The adjacent lymph nodes will be eradicated in both total and subtotal gastrectomies. This becomes

the most vital fragment of surgical operation. The accomplishment of the surgery is directly associated with the number of lymph nodes, the surgeon eradicates. In the US, it is suggested that a minimum of 15 lymph nodes are eradicated by a surgeon during gastrectomy, which is termed as D1 lymphadenectomy. In Japan, surgeons achieved a greater rate of success by eradicating a much greater number of lymph nodes located nearby cancer, which is termed as D2 lymphadenectomy (Märkl *et al.*, 2011).

Palliative Surgery for unresectable cancer

Gastric bypass (gastrojejunostomy)

The Tumors located in the stomach's inferior portion might ultimately become bulky enough and prevents food from departing from the stomach. One possibility for treating this problem is to bypass the stomach lower portion, which is performed by connecting the part of the small intestine i.e., the jejunum, to the stomach's upper portion, which helps the food particles to reach small intestine from the stomach by this new connecting link.

Endoscopic tumor ablation

In a few situations, like those in individuals with no proper health conditions to bear surgery, an endoscopic tube, which is a flexible, elongated tube, is passed through the throat. It helps to navigate the laser beam in order to vaporize the portions of the tumor. It is performed to cease haemorrhage and to remove obstruction without performing surgical procedures.

Stent placement

One more approach that keeps the tumor from obstructing the opening at the starting or terminal part of the stomach is by application of an endoscopic practice for placing a stent i.e., a metal hollow tube in that opening, which keeps the hole open allowing foods to go through it (Ell *et al.*, 1994), (see Figure 8).

Probable complications and adverse effects of surgery

Performing Surgery involves haemorrhage, clotting of blood, and injury to organs close by due to surgical procedures. In rare situations, the leakage might occur at new connecting links developed between the ends of the stomach and oesophagus and small intestine.

There is a great improvement in Surgical methods in the last few years. The mortality rate of 1% to 2% of individuals due to surgical operations for GC. The count increases when the procedure is further widespread and the exact replica of the lymph nodes is eradicated.

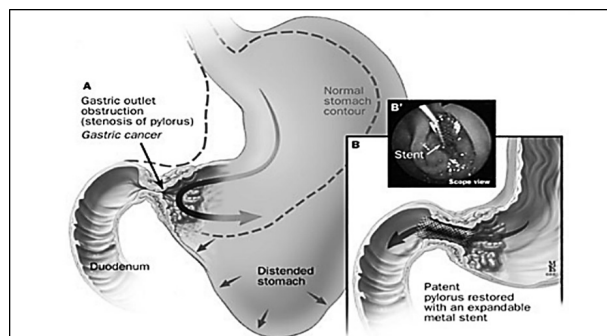


Figure 8: Endoscopic palliation of gastric outlet obstruction with an expandable metal stent; A, Gastric obstruction; B, Placement of the stent; B', Endoscopic view

After conducting a subtotal or total gastrectomy, food restriction is directed to prevent from eating or drinking for a few days, to confirm that there are no leakages in portions that are subjected to stitching during the surgical procedure.

Adverse reactions that might occur in people after getting recovered from surgery are heartburn, nausea, diarrhea, and abdominal pain, predominantly after the intake of food.

Vitamin deficiency is seen in GC patients because of less absorbed through the gastric wall.

CHEMOTHERAPY FOR STOMACH CANCER

In Chemotherapy (chemo), anti-cancer drugs are administered into the vein or through oral route in the form of pills. This makes the chemo approach as a helpful treatment for cancers that have been extended to organ tissues from the point of its origin (Hubbard *et al.*, 1986). The means by which a Chemo could be given to treat GC are Neoadjuvant and adjuvant. Chemotherapy can be administered earlier to surgery for GC, this is called Neoadjuvant treatment which leads to shrinkage of cancer cells and makes surgery easy. It often prevents the reoccurrence of cancer and thus increases the survival rate of treated people. For a few stages of GC, neoadjuvant chemotherapy is included in principle treatment choices. Frequently, chemo is usually administered again post-surgery known as Adjuvant treatment. The main purpose of this adjuvant therapy is to kill any leftover tumor cells, that help to prevent the reoccurrence of GC. Sometimes, to treat GC, chemotherapy may be provided along with radiation therapy after performing the surgery. This combination is known as chemoradiation. This approach helps to remove cancers that cannot be eradicated entirely through surgical procedures. The advantage of chemotherapy might be

provided as the main (primary) mode of treatment for GC that has been extended (metastasized) to organs at distant locations. This chemo reduces the symptoms in a few people and ultimately increases their life span. Following are the chemo drugs helpful for treating GC (Pozzo and Barone, 2008),(See Tables 2 and 3).

1. Capecitabine (Xeloda)
2. 5-FU (fluorouracil), usually administered together with leucovorin (folinic acid)
3. Cisplatin
4. Carboplatin
5. Epirubicin (Ellence)
6. Docetaxel (Taxotere)
7. Oxaliplatin (Eloxatin)
8. Irinotecan (Camptosar)
9. Trifluridine and tipiracil (Lonsurf), a combination drug in pill form
10. Paclitaxel (Taxol)

Few widespread combinations of drug use when planning a surgical operation includes,

1. Paclitaxel or Docetaxel plus either Capecitabine or 5-FU, in combination with radiation as treatment earlier to a surgical operation.
2. ECF (Epirubicin, Cisplatin, and 5-FU), which might be administered before and after surgery
3. Paclitaxel and Carboplatin, both combined with radiation as treatment earlier to a surgical operation.
4. Cisplatin plus either Capecitabine OR 5-FU, in combination with radiation as treatment earlier to surgical operation.

After surgery, if chemotherapy is provided along with radiation, a single drug such as capecitabine or 5-FU can be utilized. For the treatment of advanced GC, ECF (Epirubicin, Cisplatin, and 5-FU) can be used. Few other drug combinations might also be helpful, which includes

Cisplatin plus Irinotecan

DCF (Docetaxel, Cisplatin, and 5-FU)

Trifluridine and Tipiracil (Lonsurf), a combination drug in the form of pills

5-FU or Capecitabine plus Irinotecan,

5-FU or Capecitabine plus Oxaliplatin .

Adverse reactions of chemotherapy

Chemo drugs usually attack those cells that divide rapidly. This is how they exert their action on cancerous cells. But there are some cells in the human body that divides rapidly, for instance, cells in the linings of intestines and mouth, bone marrow and the hair follicles. Those cells may get affected by chemotherapy. Short-term adverse reactions commonly occurring due to most chemotherapy drugs include Loss of appetite, Nausea and vomiting, Loss of hairs, increase in the chance of infection due to lack of WBC, Fatigue and shortness of breath due to deficiency of RBC, Haemorrhage or bruising after minor cuts or injuries due to scarcity of platelets.

Targeted Therapies for Stomach Cancer

When chemotherapy drugs don't work, the next step adopted is Targeted therapy drugs. Chemo drugs usually attack those cells that multiply quickly i.e., which makes them be effective in tumor cells. But few other properties of cancer cells differentiate them from regular cells. Now research investigators synthesized novel drugs to address variances.

Trastuzumab

Approximately, out of 5 GC cases, 1 case exhibits excessive levels of HER2 (Human Epidermal growth factor Receptor 2), a Growth-Promoting Protein tumor cell surfaces. Cancers expressing elevated HER2 levels are known as HER2-Positive. Trastuzumab (Herceptin) is a type of Monoclonal Antibody that is effective in targeting HER2 protein. It is a human-made form of most specific immune system protein. Administration of Trastuzumab plus chemotherapy is effective in a few people with advanced cancer, HER2- positive GC when compared to chemotherapy. The survival rate is high. Adverse reactions of trastuzumab are comparatively mild. Administration of this drug plus few chemotherapy drugs such as anthracyclines like doxorubicin (Adriamycin) or epirubicin (Ellence) elevates the intensity of damage to the heart (Bang *et al.*, 2010).

Ramucirumab

Cancers require the establishment of new blood vessels to obtain nutrients and blood for their growth and proliferation. Vascular Endothelial Growth Factor (VEGF) is the protein that directs the human body to form new blood vessels by binding to the receptors to carry out their activities. Ramucirumab (Cyramza[®]) is a mAb that is able to bind to receptors for VEGF and it helps to stop the binding of VEGF to the cell surface proteins (receptors) and finally stops

the development of new blood vessels. Thus, prevents the growth and proliferation of cancer.

It is administered as an intravenous infusion (IV) every 2 weeks. A frequent adverse reaction for Ramucirumab includes diarrhea, hypertension, and headache. Severe haemorrhage, the formation of openings in intestines or stomach, and thrombus formation occur rarely but are serious. (Fuchs *et al.*, 2014).

Immunotherapy for Stomach Cancer

Immunotherapy involves the usage of drugs which helps the immune system of the patient to identify and destroy the cancerous cells.

Cancer Immunotherapy

Immunotherapy is the type of treatment which utilizes determined portions of the individual's immune system for the purpose of fighting against disease conditions, like cancers. It could be carried out in the following two ways,

1. Stimulation of human's self-immune system for working hard or in a smart way to destroy cancer cells.
2. Providing Immune system components, like human-made Immune system protein components.

Since the last few years, immunotherapy became a significant approach for the cure of various cancers like GC. The function of the immune system,

1. An immune system is a group of special cells, substances, and organs that aid in protecting the human body from infectious diseases.
2. In case any unknown or new substances (foreign) enters the body; an alarm is raised and makes the immune system to attack them. These substances may be germs (containing certain proteins) or cancer cells.

Sometimes the immune system faces a tough time to target cancer cells. This might be due to the following reasons,

1. In a few situations, the immune system may not identify cancer cells as foreign.
2. Even if cancer cells are recognized, the immune response may not be that tough to destroy the cancer cells.

To overcome these issues, research persons developed approaches that assistance the immune system to identify cancer cells and elevates its responses for the complete destruction of cancer cells.

Types of Cancer Immunotherapy

Various forms of immunotherapy for treating cancer are,

Monoclonal antibodies

They are human-made forms of immune system proteins that attack the most definite component of a cancer cell.

Cancer vaccines

They are components introduced into the human body that would initialize an immune response against a few diseases.

Immune checkpoints inhibitors

They are drug substances that usually take the "brakes" off the immune system so that it can identify and destroy those cancer cells.

Non-specific immunotherapies

This therapy strengthens the immune response to terminate the tumor cells.

Immune checkpoint inhibitors

The significant role of the human immune system is its capability of keeping itself from destroying regular body cells. To carry out this, it employs "checkpoints" which are molecules located on cells of the immune system, which are supposed to be switched on or off to initiate an immune response. Cells of GC save themselves from the attack of the immune system by using those checkpoints. But new medicines are developed that can target those checkpoints and helps a lot in treating of GC.

Immune checkpoint inhibitors to treat cancer

Drugs that target PD-1 or PD-L1

PD-1

(Programmed cell death protein 1), is a checkpoint protein located on cells of the immune system known as T cells. It usually behaves like an "off switch" which helps in keeping the T cells from destroying the normal cells of the human body. This is done when it gets attached to PD-L1 (Programmed death-ligand 1), which is a protein component located on normal and in few cases, on cancer cells also. Binding of PD-1 to PD-L1 makes T cell to leave the other cell un-attacked. But certain cancer cells possess a huge quantity of PD-L1, which helps in avoiding the attacks from the immune system. Monoclonal antibodies targets either PD-L1 or

Table 2: Chemo drugs for treating gastric cancer

Sl. No	Drug	US Brand Name	Application	Details
1	Docetaxel	Taxotere	Docetaxel is accepted to use alone or with other drugs to cure non-small cell lung cancer, breast cancer, squamous cell carcinoma of head and neck, prostate cancer, stomach adenocarcinoma or gastroesophageal junction adenocarcinoma	Semi-synthetic, 2 nd generation taxane obtained from European yew tree <i>Taxus baccate</i> . Potent and broad antineoplastic properties.
2	Fluorouracil injection	Efudex	To cure colorectal cancer, breast cancer, pancreatic cancer, gastric cancer.	Also called 5-FU. An antimetabolite fluoropyrimidine analog of nucleoside pyrimidine with antineoplastic activity. It hinders cell growth by getting incorporated into DNA and RNA
3	Trifluridine and Tipiracil Hydrochloride	Lonsurf	To treat colorectal cancer and stomach adenocarcinoma or gastroesophageal junction adenocarcinoma.	An orally bioavailable combination agent composed of the cytotoxic pyrimidine analog trifluridine (5-trifluoro-2'-deoxythymidine or TFT) and a thymidine phosphorylase inhibitor (TPI) tipiracil hydrochloride, in a molar ratio of 1.0:0.5 (TFT: TPI), with potential antineoplastic activity
4	Capecitabine	Xeloda	To treat breast cancer and stage-3 colorectal cancer. Used as first-line therapy for patients with metastatic colorectal cancer	A fluoropyrimidine carbamate belonging to the class of antineoplastic agents called antimetabolites. As a prodrug, capecitabine is selectively activated by tumor cells to its cytotoxic moiety, 5-fluorouracil (5-FU).
5	Epirubicin hydrochloride	Ellence	Used with other drugs to treat gastric cancer and breast cancer.	The hydrochloride salt of the 4'-epi-isomer of the anthracycline antineoplastic antibiotic doxorubicin. Introduces into DNA and interacts with topoisomerase II, thus obstructing DNA replication and repair and RNA and protein synthesis.
6	Irinotecan HCL	Camptosar	Used alone or with other drugs to treat colorectal cancer and other cancers like gastric cancer. Available as irinotecan HCL liposome.	The hydrochloride salt of a semisynthetic derivative of camptothecin, a cytotoxic, quinoline-based alkaloid derived from the Asian tree <i>Camptotheca acuminata</i> . Hinders topoisomerase 1 activity, DNA replication and triggers apoptotic cell death.

Table 3: Chemodrugs for treating gastric cancer(Continued from Table 2)

Sl. No.	Drug	US Brand Name	Application	Details
7	Paclitaxel	Taxol	To cure breast cancer, AIDS-related Kaposi sarcoma, ovarian cancer, non-small lung cancer, and stomach cancer. Available as paclitaxel albumin-stabilized nanoparticle formulation.	A compound derived from the Pacific yew tree <i>Taxus brevifolia</i> with antineoplastic activity. Paclitaxel binds to tubulin and prevents the disassembly of microtubules, thus resulting in the inhibition of cell division.
8	Oxaliplatin	Eloxatin	To treat gastric cancer, colorectal cancer, and stage-3 colon cancer.	An organoplatinum complex in which the platinum atom is complexed with 1,2-diaminocyclohexane (DACH) and with an oxalate ligand as a 'leaving group'. Results in inhibition of DNA replication and transcription and cell-cycle nonspecific cytotoxicity.

PD-1 and block the binding and finally strengthens the immune response against cancers.

PD-1 inhibitors

These drugs target PD-1 They are,

1. Nivolumab (Opdivo)
2. Cemiplimab (Libtayo)
3. Pembrolizumab (Keytruda)

Pembrolizumab (Keytruda)

Pembrolizumab lifts the immune response to attack cancer cells by blocking PD-1. It helps in shrinkage or slowing down the growth of cancer cells. This drug is effective in patients who are in the Advanced GC stage.

Nivolumab

Nivolumab is a wholly human immunoglobulin G4 Mab. It received FDA approval for the cure of non-

small cell lung cancer, advanced renal cell carcinoma, unresectable or metastatic melanoma, and Hodgkin lymphoma. In phase I/II CheckMate-032 study patients with advanced or metastatic GC or GEJ cancer were treated with nivolumab or nivolumab plus ipilimumab. The nivolumab/ ipilimumab combination is FDA-approved for advanced metastatic melanoma. Further clinical trials for treating of GC are ongoing ([Nagaich, 2018](#)).

PD-L1 inhibitors

These drugs usually target PD-L1. They are,

1. Avelumab (Bavencio)
2. Durvalumab (Imfinzi)
3. Atezolizumab (Tecentriq)

Drugs that target CTLA-4

CTLA-4 (Cytotoxic T-lymphocyte-associated protein 4)

Is another type of protein located on some T cells. They act as a kind of “off switch” that keeps the immune system in check.

Ipilimumab (Yervoy)

Is a type of Mab that gets attached to CTLA-4 and prevents it from carrying out its actions. Thus, it boosts the immune response against cancer cells. It is utilized to cure skin melanoma and a few other cancers (Pardoll *et al.*, 2013).

Radiation Therapy for Gastric Cancer

Radiation therapy utilizes particles or rays of high energy to destroy cells of GC in the specified location of the human body. Radiation therapy may be utilized in various ways in the treatment of GC,

In the case of a few cancers, prior to surgical operation, radiation therapy is utilized together with chemotherapy or chemo drugs to cause shrinkage of cancer cells. This makes the performance of surgery easy

After surgical treatment, radiation therapy may be done to destroy the little residues of the cancer. A combination of Radiation therapy with chemo drugs like 5-FU might help in delaying and preventing recurrence of cancer after surgical procedures

Radiation therapy can affect the growth of cancers and causes relaxation of symptoms of advanced gastric cancer, for example, haemorrhage, eating problems and pain.

External beam radiation therapy

It is usually employed for treating GC. This approach concentrates the radiation on the cancer cells, emitted by a machine located external to the human body. Distinct varieties of external beam radiation like Three-dimensional conformal radiation therapy (3D-CRT) and Intensity-modulated radiation therapy (IMRT) are employed. They need computer systems and unique procedures for focussing the radiation over the cancer cells and to reduce the intensity of damage to adjacent normal cells and organs (Hubbard *et al.*, 1986).

Before starting the treatment, the expert persons would collect careful measurements to figure out the exact angles to focus the radiation beams and to decide the desired radiation dose required. This planning session is known as Simulation, which generally comprises obtaining imaging tests like CT or MRI (Magnetic Resonance Imaging) scans. Radiation therapy is more like obtaining an x-ray, but the intensity of radiation is stronger. It is a painless treatment. Each therapy may require just a few minutes, even though the setup time, which involves making the patient ready for therapy is quite longer.

Treatment is frequently provided for 5 days in a week for some weeks or months. Adverse reactions become too serious when radiation therapy is combined with chemo drugs. People face problems while eating and drinking. Liquid nutrition is provided through intravenous infusions or by feeding tube approach during therapy. Radiation therapy may cause damage to adjacent organ tissues leading damage to the heart and lungs.

Recurrent Gastric Cancer

Recurrent GC is cancer that has reappeared after it has been cured. Cancer might recur in the stomach or in other body parts like the liver or lymph nodes (Hubbard *et al.*, 1986).

Follow-up tests

Few tests must be done continuously after the treatment was performed. The results of those tests will tell whether the condition of the patient has transformed or cancer has recurred. Such tests are known as Follow-Up Tests or Check-Ups.

Further tests might also be done,

Carcinoembryonic antigen (CEA) assay and CA 19-9 assay .In this assay method, an examination of sample tissue is done to determine the number of specific substances made by tissues, organs, or cancer cells in the human body. Those specific substances are connected to specific kinds of cancer when detected at elevated levels in the human body. They are termed as tumor-markers. Higher than normal levels of carcinoembryonic (CEA) and CA 19-9 might indicate that GC has come back after therapy.

Treatment Options by Stage

Stage 0 (Carcinoma in Situ)

Treatment for stage 0 is generally surgery (total or subtotal gastrectomy)

Stage I Gastric Cancer

Treatment for Stage I Gastric Cancer may involve the below approaches,

1. Surgery (total or subtotal gastrectomy).
2. Surgery (total or subtotal gastrectomy) followed by chemoradiation therapy.
3. A clinical trial of chemoradiation therapy provided before surgery.

Stage II Gastric Cancer

Treatment for Stage II Gastric Cancer may involve the below approaches,

1. Surgery (total or subtotal gastrectomy).
2. Surgery (total or subtotal gastrectomy) followed by chemoradiation therapy or chemotherapy.
3. Chemotherapy is administered before and after surgery.
4. A clinical trial of surgery followed by chemoradiation therapy testing new anticancer drugs.
5. A clinical trial of chemoradiation therapy provided before surgery.

Stage III Gastric Cancer

Treatment for stage III Gastric Cancer may involve the below approaches,

1. Surgery (total gastrectomy).
2. Surgery followed by chemoradiation therapy or chemotherapy.
3. Chemotherapy is administered before and after surgery.
4. A clinical trial of surgery followed by chemoradiation therapy testing new anticancer drugs
5. A clinical trial of chemoradiation therapy provided before surgery.

Stage IV and Recurrent Gastric Cancer

Treatment for stage IV or recurrent gastric cancer may involve the below approaches,

1. Chemotherapy as palliative therapy to relieve symptoms and improve the quality of life.
2. Targeted therapy with a monoclonal antibody with or without chemotherapy
3. Immunotherapy
4. Endoluminal laser therapy or endoluminal stent placement to relieve a blockage in the stomach, or gastrojejunostomy to bypass the blockage
5. Radiation therapy as palliative therapy or to cause shrinkage of a tumor that blocks the stomach.
6. Surgery as palliative therapy to stop haemorrhage or to cause shrinkage of a tumor that blocks the stomach
7. A clinical trial of new combinations of chemotherapy as palliative therapy to relieve symptoms and improve the quality of life ([Hubbard et al., 1986](#)).

CONCLUSIONS

GC is a malignant disease with a generally deprived long-term prognosis. Every patient with GC needs to be treated according to the individual plan made by MDT. The planning strategy should consider the stage of the tumor, the intention of the therapy, the patient's performance status, and technical possibilities. Generally, the most beneficial approach seems to be surgery combined with chemotherapy and radiotherapy. The primary treatment approach for advanced gastric cancer has been the standard chemotherapy and the combination of cytotoxic regimens could improve the overall response rates by $\geq 40\%$; however, the median survival of the patients is still under 12 months. 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 gastric cancer. But as only about 20% of the patients with gastric cancer 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 gastric tumors. Further work needs to develop more effective and specific therapies that hopefully have fewer adverse events compared with the currently available therapeutic regimens.

Immunotherapy, the next generation of anti-cancer strategies (after surgery, chemotherapy, and radiation therapy), targeting immune checkpoints of cancer, has been actively evaluated in clinical trials and applied in clinical practice for selected cancer types.

Advancement has been made in understanding the pathogenesis and the molecular biology of gastric cancer and in optimizing the available treatment options and modalities. However, in the future, the focus should be on further unravelling the taxonomy of gastric cancer, fine-tuning treatment strategies, and developing new drugs for patients with advanced gastric cancer. In isolation comprehensive staging and evaluation with a multidisciplinary team to determine roles of neoadjuvant, perioperative, and adjuvant combination chemotherapy, surgery, and external-beam radiation therapies should be considered.

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