Cancer Association of South Africa (CANSA)

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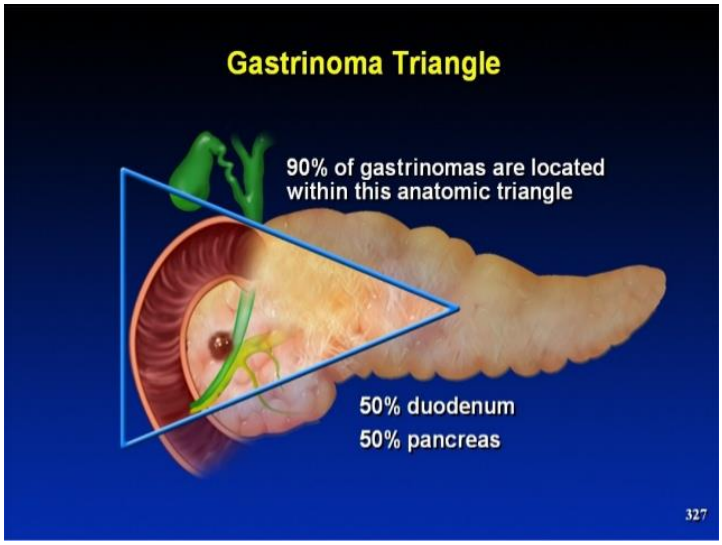
Fact Sheet
on
Gastrinoma

Introduction

A gastrinoma is a tumour in the pancreas or duodenum that secretes excess of gastrin leading to ulceration in the duodenum, stomach and the small intestine. 'Gastrin' is a peptide hormone that stimulates secretion of gastric acid (HCl) by the parietal cells of the stomach. This results in hypersecretion of the hydrochloric acid (HCl) into the duodenum, which causes the ulcers. Excessive HCl production also causes hyperperistalsis (increased motility), and inhibits the activity of lipase, causing severe diarrhoea.



[Picture Credit: Gastrinoma Triangle]

The parietal cells of the stomach (also known as oxyntic or delomorphous cells), are the epithelial cells that secrete hydrochloric acid (HCl) and intrinsic factor. These cells are located in the gastric glands found in the lining of the fundus and in the body of the stomach.

Gastrinoma is usually found in the pancreas, although it may arise in the stomach or duodenum. Those occurring in the pancreas have a greater potential for malignancy. Most gastrinomas are found in the gastrinoma triangle; this is bound by the junction of cystic and common bile ducts, junction of the second and third parts of the duodenum, and the junction of the neck and body of the pancreas.

Gastrinoma is also referred to as Zollinger-Ellison (ZES) syndrome.
(UpToDate; Wikipedia).

Gastrinoma

The annual incidence of gastrinomas is 0.5 to 2 per million of the population. Most patients are diagnosed between the ages of 20 and 50, with a higher incidence in men as compared

with women. Approximately 80 percent of gastrinomas are sporadic, but 20 to 30 percent occur in association with multiple endocrine neoplasia type 1 (MEN1). Although gastrinomas are one of the most common functional pancreatic neuroendocrine tumours, only 25 percent of gastrinomas arise in the pancreas. Approximately 50 to 88 percent of patients with sporadic ZES, and 70 to 100 percent of patients with ZES associated with MEN1, have duodenal gastrinomas. Duodenal gastrinomas are predominantly found in the first part of the duodenum. As compared with pancreatic gastrinomas, duodenal gastrinomas are usually small (<1 cm), are often multiple, and are less likely to have metastasized to the liver at diagnosis (0 to 10 versus 22 to 35 percent). In 5 to 15 percent of patients, gastrinomas arise in non-pancreatic, non-duodenal abdominal (stomach, peripancreatic lymph nodes, liver, bile duct, ovary), and extra-abdominal (heart, small cell lung cancer) locations.
(UpToDate).

Gastrinoma is a type of pancreatic neuroendocrine tumour, which is a rare endocrine tumour that occurs sporadically as well as part of inherited familial endocrine syndromes such as Multiple Endocrine Neoplasia Type-1 (MEN-1).

Gastrinoma is often associated with increased stomach acid as part of the Zollinger-Ellison Syndrome (ZES). ZES is a condition where increased production and release of stomach acid is associated with the formation of ulcers. This is an uncommon cause of stomach and duodenal ulcers (peptic ulcers) as most are actually caused by bacteria called *Helicobacter pylori (H. pylori)*. Most peptic ulcer disease caused by *H. pylori* can be treated effectively with acid reducing medications and antibiotics.

ZES can be distinguished from the common cause of peptic ulcer disease in most cases, namely the presence of multiple or atypical ulcers. Atypical or multiple ulcers strongly suggest the diagnosis of ZES and therefore a gastrinoma, however, in 18% to 25% of patients no ulcers are present at the time of diagnosis.
(The American Association of Endocrine Surgeons).

Incidence of Gastrinoma in South Africa
The National Cancer Registry (2012) does not provide information on the incidence of gastrinoma.

Signs and Symptoms of Gastrinoma
Symptoms associated with gastrinomas are usually nonspecific and can mimic other gastrointestinal (GI) disorders. Abdominal pain is the most common symptom, occurring in 70% of patients. Less common symptoms include diarrhoea (in 10% to 30% of patients), nausea, and vomiting.

However, certain symptoms and signs should raise the suspicion of a gastrinoma, especially if they develop while the patient is receiving adequate acid-suppressing medication:

- Recurrent ulcers after medical or surgical treatment
- Gastric bleeding
- Intestinal perforation
- Gastric outlet obstruction
- Abdominal pain – caused by a stomach or duodenal ulcer
- Diarrhoea

- Indigestion (heartburn)
- Feeling and being sick
- Weight loss

(Department of Surgery, University of Arizona; Cancer Research UK)

Differential Diagnosis of Gastrinoma

Patients with hypergastrinaemia (abnormally high gastrin levels) do not necessarily have a gastrinoma. Before a patient is diagnosed with a gastrinoma, the following conditions should be ruled out:

Increased gastric acid secretion

- Antral hyperplasia
- Retained antrum
- Gastric outlet obstruction
- Renal failure
- Short bowel syndrome

Low or no gastric acid secretion

- Pernicious anaemia
- Chronic atrophic gastritis
- Hypochlorhydria
- Vagotomy
- *Helicobacter pylori* gastritis

(Department of Surgery, University of Arizona).

Diagnosis of Gastrinoma

The diagnosis should be suspected on the basis of the clinical presentation and established in almost all patients by demonstrating elevated basal gastric acid secretion (BAO) and fasting elevations of the protein gastrin, which is produced by the gastrinoma. It is the protein gastrin, which leads to the increased acid secretion causing the ulcer formation. ZES should be suspected in the clinical setting of peptic ulcer with diarrhoea, familial peptic ulcer, peptic ulcer in unusual locations, and recurrent or resistant peptic ulcers after treatment.

ZES should be particularly suspected in patients with:

- peptic ulcers that persist or recur despite treatment for *H. pylori* infection or with histamine H_2-receptor antagonists
- severe oesophagitis
- duodenal ulcers without *H pylori*.

Gastrinomas may behave in a benign or malignant fashion. The percentage of gastrinomas that are actually malignant is unclear. No visual microscopic (histologic) criteria can predict malignancy. Malignancy can only be established by the behaviour of the gastrinoma leading to the presence of metastases.

Approximately one half of patients have a malignant behaving gastrinoma at the time of diagnosis. Metastases are usually found in the lymph nodes near the pancreas and in the

liver. Bone metastases have been reported in about 30% of patients with metastatic gastrinoma in the liver. A number of cases of gastrinoma localised in lymph nodes have been described with no evidence of primary tumour. Some of these cases have been apparently cured by excision of lymph nodes, which suggests that the gastrinoma was not metastatic but originated as a primary tumour in the lymph node.

Other tests may include

- CT scan
- MRI scan
- Endoscopic ultrasound – this is the same as an endoscopy but using an ultrasound scan
- PET scan
- Radioactive scan (octreoscan)

An octreoscan is also sometimes called somatostatin receptor scintigraphy (SSRS). The patient has an injection of a substance called octreotide and then has a scan using a special type of scanner. Octreotide is taken up by some neuroendocrine tumour cells. Doctors can attach a radioactive substance to the octreotide that shows up on the scan.
(Cancer Research UK; The American Association of Endocrine Surgeons).

Staging of Gastrinoma
Elements for Staging Gastrinoma:

Tx Primary tumour cannot be assessed
T0 No primary tumour at operation or imaging
T1 Primary tumour < 1 cm
T2 Primary tumour 1.1-2 cm
T3 Primary tumour 2.1-2.9 cm
T4 Primary tumour > 3 cm

Nx Lymph nodes cannot be assessed
N0 No lymph node metastases
N1 Lymph node metastases

Mx Distant metastases cannot be assessed
M0 No distant metastases
M1 Distant metastases

Stage	Tumour	Lymph Node	Distant Metastases
0	T0	N0	M0
I	T1 T2	Any N	M0
II	T3 T4	Any N	M0
III	Any T	Any N	M1

(Haley Gallup).

Treatment of Gastrinoma
The treatment of gastrinoma has both a medical and surgical component.

Medical treatment of gastrinoma
Individualise the selection of treatment. Base treatment on factors related to ulcer disease, diarrhoea, and malignant properties of the tumour. Antisecretory medications are helpful for controlling the manifestations of peptic acid disease and secretory diarrhoea (secondary to hyperacidity).

- Proton pump inhibitors (e.g. omeprazole, lansoprazole)
  - These are highly effective drugs and are the drugs of choice for suppressing acid secretion. Long duration of action, fewer adverse effects, and high potency make them superior to H2 blockers.
  - In 60% of patients, ulcer healing occurs within 2 weeks. In 90-100% of patients, healing occurs within 4 weeks.
  - The recommended initial dose of omeprazole is 60 mg/d. Divided, twice-a-day dosing is suggested for doses greater than 80 mg/d. Once an effective maintenance dose is achieved, tapering of the medication, while monitoring symptoms and acid output, is suggested.

- H2-receptor antagonists
  - The dose usually is 4-8 times higher than the dose administered to patients with peptic ulcer disease.
  - Although a good success rate exists, this treatment has been reported to fail in 50% of patients.

- Chemotherapy
  - This is indicated in patients with metastatic disease and in patients who are not candidates for surgery; however, it is not indicated for metastatic disease confined to the lymph nodes.
  - Chemotherapy reduces tumour size and improves the symptoms secondary to metastatic effects of the tumour.
  - A combination of streptozocin, 5-fluorouracil, and doxorubicin has been used, with the response rate reported to be as high as 65%.
  - Granberg. *et al.,* described a patient with almost complete response on treatment with Sandostatin LAR, a long-acting somatostatin analogue.
  - Interferon or targeted radiotherapy may also be considered in patients who are not candidates for chemotherapy.

(Medscape).

Surgical treatment of gastrinoma
Treatment of choice for gastrinoma is to remove the surgically where possible. Peptic ulcers must be aggressively treated and controlled prior to surgery. The type of surgery for gastrinomas depends on the location of the tumour. Since these tumours may frequently occur at more than one spot in the pancreas and the surrounding tissues more than one procedure may be required. The following operative procedures may be utilized to treat gastrinomas.

- Enucleation: Many small gastrinomas in the pancreas may be treated by enucleation alone. This is a procedure of choice for patients that have small tumours (less than 1cm) where the tumour is located on the surface of the pancreas.

- Resection of the pancreas: in patients with large tumours a distal pancreatectomy or a Whipple operation may be indicated depending on where the tumour is located in the pancreas.
- Duodenal exploration: Gastrinomas often occur in the wall of the duodenum (first part of the intestine) and therefore opening duodenum and carefully feeling it to remove any tumours in this area is important.
- Lymph nodes: In some patients the tumour may be located in the lymph glands outside the pancreas, therefore, careful palpation and removal of these glands is important at the time of surgery

(Department of Surgery, Center for Pancreatic and Biliary Diseases, University of Southern California).

About Clinical Trials

Clinical trials are research studies that involve people. These studies test new ways to prevent, detect, diagnose, or treat diseases. People who take part in cancer clinical trials have an opportunity to contribute to scientists' knowledge about cancer and to help in the development of improved cancer treatments. They also receive state-of-the-art care from cancer experts.

Types of Clinical Trials

Cancer clinical trials differ according to their primary purpose. They include the following types:

Treatment - these trials test the effectiveness of new treatments or new ways of using current treatments in people who have cancer. The treatments tested may include new drugs or new combinations of currently used drugs, new surgery or radiation therapy techniques, and vaccines or other treatments that stimulate a person's immune system to fight cancer. Combinations of different treatment types may also be tested in these trials.

Prevention - these trials test new interventions that may lower the risk of developing certain types of cancer. Most cancer prevention trials involve healthy people who have not had cancer; however, they often only include people who have a higher than average risk of developing a specific type of cancer. Some cancer prevention trials involve people who have had cancer in the past; these trials test interventions that may help prevent the return (recurrence) of the original cancer or reduce the chance of developing a new type of cancer

Screening - these trials test new ways of finding cancer early. When cancer is found early, it may be easier to treat and there may be a better chance of long-term survival. Cancer screening trials usually involve people who do not have any signs or symptoms of cancer. However, participation in these trials is often limited to people who have a higher than average risk of developing a certain type of cancer because they have a family history of that type of cancer or they have a history of exposure to cancer-causing substances (e.g., cigarette smoke).

Diagnostic - these trials study new tests or procedures that may help identify, or diagnose, cancer more accurately. Diagnostic trials usually involve people who have some signs or symptoms of cancer.

Quality of life or supportive care - these trials focus on the comfort and quality of life of cancer patients and cancer survivors. New ways to decrease the number or severity of side

effects of cancer or its treatment are often studied in these trials. How a specific type of cancer or its treatment affects a person's everyday life may also be studied.

Where Clinical Trials are Conducted

Cancer clinical trials take place in cities and towns in doctors' offices, cancer centres and other medical centres, community hospitals and clinics. A single trial may take place at one or two specialised medical centres only or at hundreds of offices, hospitals, and centres.

Each clinical trial is managed by a research team that can include doctors, nurses, research assistants, data analysts, and other specialists. The research team works closely with other health professionals, including other doctors and nurses, laboratory technicians, pharmacists, dieticians, and social workers, to provide medical and supportive care to people who take part in a clinical trial.

Research Team

The research team closely monitors the health of people taking part in the clinical trial and gives them specific instructions when necessary. To ensure the reliability of the trial's results, it is important for the participants to follow the research team's instructions. The instructions may include keeping logs or answering questionnaires. The research team may also seek to contact the participants regularly after the trial ends to get updates on their health.

Clinical Trial Protocol

Every clinical trial has a protocol, or action plan, that describes what will be done in the trial, how the trial will be conducted, and why each part of the trial is necessary. The protocol also includes guidelines for who can and cannot participate in the trial. These guidelines, called eligibility criteria, describe the characteristics that all interested people must have before they can take part in the trial. Eligibility criteria can include age, sex, medical history, and current health status. Eligibility criteria for cancer treatment trials often include the type and stage of cancer, as well as the type(s) of cancer treatment already received.

Enrolling people who have similar characteristics helps ensure that the outcome of a trial is due to the intervention being tested and not to other factors. In this way, eligibility criteria help researchers obtain the most accurate and meaningful results possible.

National and International Regulations

National and international regulations and policies have been developed to help ensure that research involving people is conducted according to strict scientific and ethical principles. In these regulations and policies, people who participate in research are usually referred to as "human subjects."

Informed Consent

Informed consent is a process through which people learn the important facts about a clinical trial to help them decide whether or not to take part in it, and continue to learn new information about the trial that helps them decide whether or not to continue participating in it.

During the first part of the informed consent process, people are given detailed information about a trial, including information about the purpose of the trial, the tests and other procedures that will be required, and the possible benefits and harms of taking part in the trial. Besides talking with a doctor or nurse, potential trial participants are given a form, called an informed consent form, that provides information about the trial in writing. People who agree to take part in the trial are asked to sign the form. However, signing this form does not mean that a person must remain in the trial. Anyone can choose to leave a trial at any time—either before it starts or at any time during the trial or during the follow-up period. It is important for people who decide to leave a trial to get information from the research team about how to leave the trial safely.

The informed consent process continues throughout a trial. If new benefits, risks, or side effects are discovered during the course of a trial, the researchers must inform the participants so they can decide whether or not they want to continue to take part in the trial. In some cases, participants who want to continue to take part in a trial may be asked to sign a new informed consent form.

New interventions are often studied in a stepwise fashion, with each step representing a different "phase" in the clinical research process. The following phases are used for cancer treatment trials:

Phases of a Clinical Trial

Phase 0. These trials represent the earliest step in testing new treatments in humans. In a phase 0 trial, a very small dose of a chemical or biologic agent is given to a small number of people (approximately 10-15) to gather preliminary information about how the agent is processed by the body (pharmacokinetics) and how the agent affects the body (pharmacodynamics). Because the agents are given in such small amounts, no information is obtained about their safety or effectiveness in treating cancer. Phase 0 trials are also called micro-dosing studies, exploratory Investigational New Drug (IND) trials, or early phase I trials. The people who take part in these trials usually have advanced disease, and no known, effective treatment options are available to them.

Phase I (also called phase 1). These trials are conducted mainly to evaluate the safety of chemical or biologic agents or other types of interventions (e.g., a new radiation therapy technique). They help determine the maximum dose that can be given safely (also known as the maximum tolerated dose) and whether an intervention causes harmful side effects. Phase I trials enrol small numbers of people (20 or more) who have advanced cancer that cannot be treated effectively with standard (usual) treatments or for which no standard treatment exists. Although evaluating the effectiveness of interventions is not a primary goal of these trials, doctors do look for evidence that the interventions might be useful as treatments.

Phase II (also called phase 2). These trials test the effectiveness of interventions in people who have a specific type of cancer or related cancers. They also continue to look at the safety of interventions. Phase II trials usually enrol fewer than 100 people but may include as many as 300. The people who participate in phase II trials may or may not have been treated previously with standard therapy for their type of cancer. If a person has been treated previously, their eligibility to participate in a specific trial may depend on the type and amount of prior treatment they received. Although phase II trials can give some indication of whether

or not an intervention works, they are almost never designed to show whether an intervention is better than standard therapy.

Phase III (also called phase 3). These trials compare the effectiveness of a new intervention, or new use of an existing intervention, with the current standard of care (usual treatment) for a particular type of cancer. Phase III trials also examine how the side effects of the new intervention compare with those of the usual treatment. If the new intervention is more effective than the usual treatment and/or is easier to tolerate, it may become the new standard of care.

Phase III trials usually involve large groups of people (100 to several thousand), who are randomly assigned to one of two treatment groups, or "trial arms": (1) a control group, in which everyone in the group receives usual treatment for their type of cancer, or 2) an investigational or experimental group, in which everyone in the group receives the new intervention or new use of an existing intervention. The trial participants are assigned to their individual groups by random assignment, or randomisation. Randomisation helps ensure that the groups have similar characteristics. This balance is necessary so the researchers can have confidence that any differences they observe in how the two groups respond to the treatments they receive are due to the treatments and not to other differences between the groups.

Randomisation is usually done by a computer program to ensure that human choices do not influence the assignment to groups. The trial participants cannot request to be in a particular group, and the researchers cannot influence how people are assigned to the groups. Usually, neither the participants nor their doctors know what treatment the participants are receiving.

People who participate in phase III trials may or may not have been treated previously. If they have been treated previously, their eligibility to participate in a specific trial may depend on the type and the amount of prior treatment they received.

In most cases, an intervention will move into phase III testing only after it has shown promise in phase I and phase II trials.

Phase IV (also called phase 4). These trials further evaluate the effectiveness and long-term safety of drugs or other interventions. They usually take place after a drug or intervention has been approved by the medicine regulatory office for standard use. Several hundred to several thousand people may take part in a phase IV trial. These trials are also known as post-marketing surveillance trials. They are generally sponsored by drug companies.

Sometimes clinical trial phases may be combined (e.g., phase I/II or phase II/III trials) to minimize the risks to participants and/or to allow faster development of a new intervention.

Although treatment trials are always assigned a phase, other clinical trials (e.g., screening, prevention, diagnostic, and quality-of-life trials) may not be labelled this way.

Use of Placebos

The use of placebos as comparison or "control" interventions in cancer treatment trials is rare. If a placebo is used by itself, it is because no standard treatment exists. In this case, a trial would compare the effects of a new treatment with the effects of a placebo. More often,

however, placebos are given along with a standard treatment. For example, a trial might compare the effects of a standard treatment plus a new treatment with the effects of the same standard treatment plus a placebo.

Possible benefits of taking part in a clinical trial

The benefits of participating in a clinical trial include the following:

- Trial participants have access to promising new interventions that are generally not available outside of a clinical trial.
- The intervention being studied may be more effective than standard therapy. If it is more effective, trial participants may be the first to benefit from it.
- Trial participants receive regular and careful medical attention from a research team that includes doctors, nurses, and other health professionals.
- The results of the trial may help other people who need cancer treatment in the future.
- Trial participants are helping scientists learn more about cancer (e.g., how it grows, how it acts, and what influences its growth and spread).

Potential harms associated with taking part in a clinical trial

The potential harms of participating in a clinical trial include the following:

- The new intervention being studied may not be better than standard therapy, or it may have harmful side effects that doctors do not expect or that are worse than those associated with standard therapy.
- Trial participants may be required to make more visits to the doctor than they would if they were not in a clinical trial and/or may need to travel farther for those visits.

Correlative research studies, and how they are related to clinical trials

In addition to answering questions about the effectiveness of new interventions, clinical trials provide the opportunity for additional research. These additional research studies, called correlative or ancillary studies, may use blood, tumour, or other tissue specimens (also known as 'biospecimens') obtained from trial participants before, during, or after treatment. For example, the molecular characteristics of tumour specimens collected during a trial might be analysed to see if there is a relationship between the presence of a certain gene mutation or the amount of a specific protein and how trial participants responded to the treatment they received. Information obtained from these types of studies could lead to more accurate predictions about how individual patients will respond to certain cancer treatments, improved ways of finding cancer earlier, new methods of identifying people who have an increased risk of cancer, and new approaches to try to prevent cancer.

Clinical trial participants must give their permission before biospecimens obtained from them can be used for research purposes.

When a clinical trial is over

After a clinical trial is completed, the researchers look carefully at the data collected during the trial to understand the meaning of the findings and to plan further research. After a phase I or phase II trial, the researchers decide whether or not to move on to the next phase or stop testing the intervention because it was not safe or effective. When a phase III trial is completed, the researchers analyse the data to determine whether the results have medical

importance and, if so, whether the tested intervention could become the new standard of care.

The results of clinical trials are often published in peer-reviewed scientific journals. Peer review is a process by which cancer research experts not associated with a trial review the study report before it is published to make sure that the data are sound, the data analysis was performed correctly, and the conclusions are appropriate. If the results are particularly important, they may be reported by the media and discussed at a scientific meeting and by patient advocacy groups before they are published in a journal. Once a new intervention has proven safe and effective in a clinical trial, it may become a new standard of care.
(National Cancer Institute).

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