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Review Article

Intestinal Cancer and Role of Phytochemicals

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Abstract

In Western world the intestinal cancer is becoming more common with time. The adults above the age of 50, and those drinking alcohol are at more risk as compared to others. The scientists are also working on the genetic factors associated with small intestine cancer especially colorectal cancer. Intestinal cancer includes the cancer of small intestinal as well as large intestinal parts. According to studies people affected with these cancers are at risk of getting any second cancer that might be associated with stomach, lungs, vagina or kidneys. As small intestine is directly related to digestive system the most common symptom is abdominal pain and noticeable lump in the abdomen. The treatment includes chemotherapy, 2 line chemotherapy and surgery. However surgery is considered as the pillar curative treatment. And if detected at the early stage the survival rate is increased by 50%.

Keywords: Intestinal Cancer; Phytochemicals; Small Intestinal Cancer

Introduction

Intestinal cancer is a rare infrequent cancer. (Medicine, 2020) [1]. It is caused by uncontrolled division of abnormal cells and their malignant growth in different parts of intestine i.e. duodenum, jejunum, ileac, large intestine and colon or rectal parts. Intestinal cancer accommodates in body because of consuming high fatty foods or having a medical history of Crohn's disease, celiac disease or colonic polyps (Medicine, 2020) [2]. This cancer can also spread to other tissues and organs and is fatal, however if detected at early stage the survival rate is above 50% [3]. (Society)

History

- 1895: Over 100 years ago, Dr.Aldred Warthin (Oncol, 2014,oct) Suspected the Order in an affected woman (Who subsequently died of endometrial cancer)
- 1913: First report on gynecological cancer specifically Endometrial cancer and gastrointestinal cancer
- 1925: American gastroenterologist Burill Bernard Cohn and Herman Rosenberg report the first case of Adenocarcinoma complicating ulcerative colitis (History of Colorectal cancer, retrived 7 sep 2016) [4].
- 1932: English physician Cuthbert Dukes gave a classification System for colorectal cancer (Mattar, Lough, Pishvaian, and Charabaty, 2011) [6].
- 1965: Researchers discover association of primary sclerosing Cholangitis with ulcerative colisis ("Cancer progress"., 10 sep 2016) [7].
- 1966-69: Treatment of colorectal cancer was revolutionized using Fiber colonoscopy
- 1985-91: Survival rate increased using chemotherapy
- 1990-99: Genetic tests became available for familial adenomatous and hereditary colorectal cancer (Dietz, (October 2013)) [8].
- 2000's: International collaboration for best practices of colorectal Cancer (Surgeons, Retrieved 2017-08-15.) [9].
- 2010's: In the USA, the National Accreditation Program for Rectal Cancer begins accepting applications whose goal is to Eliminate variable patient outcomes following European Model (World Cancer Report 2014. World Health Organization).

Present time

Globally it is the Third most common type of cancer making Up to 10% of all the cases Detection and treatment at early stage is more curative It is less common in women than man.

Statistical analysis

Survival by stage

The stage of cancer strongly determines the treatment and the survival. If the cancer is localized at its primary site i.e. found only in that part where it started is referred to as Stage 1.

I f the cancer has spread in different parts then is said to be Regional or Distant

- Localized: At primary site
- Regional: Spread to regional lymph nodes
- Distant: Cancer is Metastasized
- Unknown: Un staged

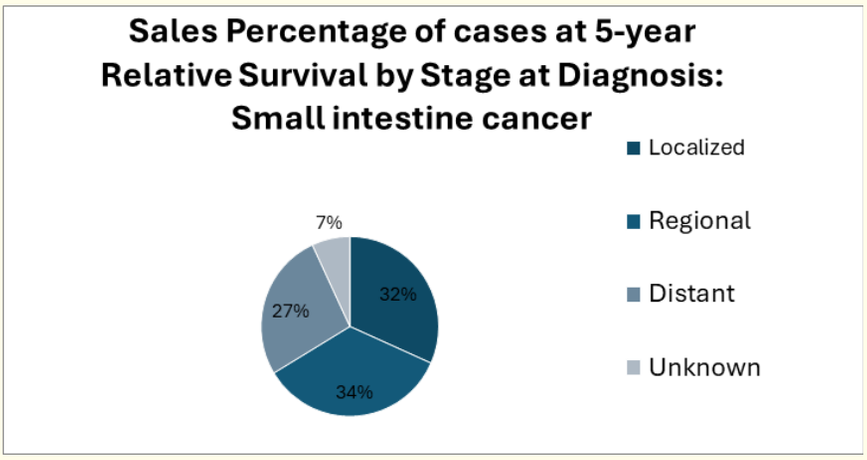

Figure a

How common is this cancer?

Small intestine is rare as compared to other cancers,

Types

Here are two main parts of intestinal cancer

Small intestinal cancer

Large intestinal cancer

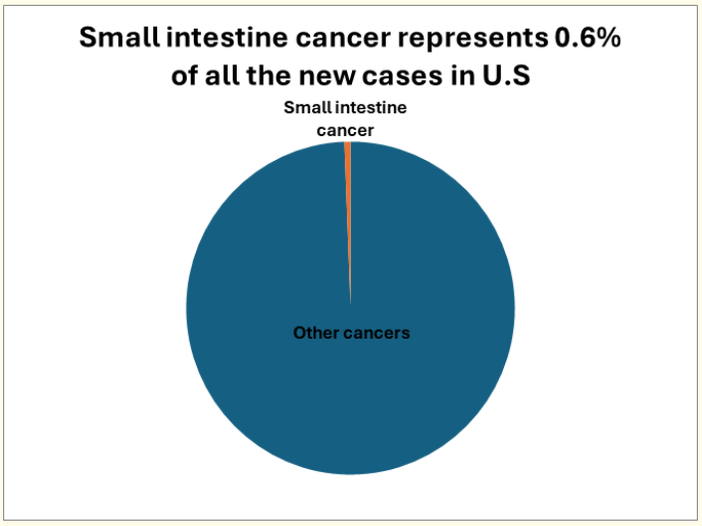

Figure b

Cancer type	Estimated cases in 2020	Estimated deaths in 2020
Small intestine cancer	11,110	1700

Table a

Small intestinal cancer

Small intestinal cancer is an infrequent cancer in which malignant (cancer) cells form

In the tissues of small intestine. There are five major sorts of intestine cancer:

- **Adenocarcinoma tumor:** This tumor is originated from glandular cells in the lining of the small intestine. Adeno means "gland" and carcinoma Is a type of cancer. Mostly occurrence of this tumor in duodenum near to the stomach. They may grow and block the intestine. More common in Males around 50-70 years of the age
- **Carcinoid:** Carcinoid is a type of neuroendocrine tumor and they tend to occur in ileum. Slow growing Tumors often taken root in the lower section of small intestine. This tumor also affected the appendix and rectum. Tumor release large amount of a chemical known as serotonin.
- **Sarcoma:** Sarcoma cancerous cells developed in the soft tissues of the small intestine. Leiomyosarcoma Is a subtype of sarcomas starts in smooth muscle of the cells in small intestine. Mostly it occurs in small intestine near the large intestine.
- **Gastrointestinal stromal Tumor (GIST):** It is rare type of small intestinal cancer. Not all GIST are cancerous. GIST occurs in any of three Part of small intestine. Certain factors affect prognosis (chance of recovery) and treatment option.
- **Lymphomas tumor:** Is also a type of cancer which starts from lymph nodes. Mostly occur in jejunum. This typical sub-type is non-Hodgkin's [10] (Onco, 2018, Oct) lymphomas People who develop them often a type of immunodeficiency disorder. This tumor badly affects defense system of our body then our body cannot fight with infections.
- **Large intestinal cancer:** Is a type of cancer which begins in large intestine (colon). Colon is the final part of digestive Tract. There are two main part of large intestine colon and rectal collectively known as colorectal when it concern with tumor this term is known as colorectal intestinal cancer There are many sorts of colorectal cancer, the foremost common of which is adenocarcinoma. Other types include carcinoid tumors, gastrointestinal stromal tumors, and colorectal lymphoma.
- **Gastrointestinal stromal cancer:** starts in the special cell wall of the muscle in a GI tract. They can be benign (noncancerous) at first, but after many turns it into cancer. When it's happening it is known as sarcomas. It occurs from esophagus to anus. 50-70% develops in stomach and around 2030% will arise in small intestine
- **Lymphoma:** start in lymph nodes which is the part of immune system, and it can also started in colon and rectal.
- **Carcinoid:** start in special hormone producing cells often they cause no symptoms and usually treated by surgery.
- **Turcot syndrome:** Rare disorders include colorectal polyposis, colon cancer and brain tumors. Due to mutation in different genes turcot syndrome is known as genetically heterogeneous.
- **Peutz-jeghers syndrome (PJS):** is an autosomal dominant disorder and it is caused by gene changing on chromosome 19 which is known as STK11, [11] (August 2019) which function as a tumors superior gene.
- **Familial colorectal cancer:** up to 15% patients of colorectal cancer have family member with same cancer. It may occur due to continue pattern of dominant autosomal gene pairs.
- **Juvenile polyposis coli:** is a childhood onset disease by repeating pattern of dominant gene of cancer causing and associated with hamartomatous.

Symptom and complications of intestinal cancer

As it is the leading cause of death, so it is very important to know its symptoms and signs.

Cancer in small intestine

Although small intestine (also called small bowel) is a large part of gastrointestinal tract [5]. but the cancers associated with small intestine are rare, infect chances of these cancers are 1in 10 cases of all the gastrointestinal. Some symptoms of cancer develop in small intestine are following [12-14].

- Results in Abdominal pain
- Fatigue or weakness
- There is a sudden weight loss
- Noticeable lump in the abdomen
- Bloody stools

Cancer in large intestine

Colon cancer which is the third leading cause of cancer related death in United States [6] has no symptoms in the early stages but become more noticeable as the cancer progress. Symptoms of colon cancers come in two general ways

- **Local symptoms:** Depends on where the tumor is located in colon
- **Systemic symptoms:** It is based on whole body

Local symptoms include abdominal discomfort and change in bowel habits.

Change in bowel habits

- Different people have different bowel habits, their stool size color and consistency is different. so it is very important to be alert if there is any change in bowel movement.
- A Consistence change in stool frequency is one of the major signs of cancer.
- Any change in the stool shape like narrow or thin stools may be the cause of cancer.
- The stool color becomes dark red due to bleeding in the colon.
- Patients also suffer from Alternating diarrhea and constipation.

Abdominal discomfort

Cramping and pain in the abdomen may also occur in those who suffer from this cancer. Cramps, most frequently, occur with advanced cancer in the left side of colon. Astumour grows and bleed in colon it irritates lining of abdomen.

Excessive gas and bloating

Gas and bloating can be a sign of intestinal cancer. But however, to pass gas 23 times a day is considered to be normal.

Nausea or vomiting is basically tumor causing bowel obstruction may result in nausea or vomiting which occur at any stage of cancer but most common with advanced cancer. However, these symptoms alone unlikely to be indication of intestinal cancer.

Systemic symptoms

These are the symptoms that affect the whole body, and are given below:

Loss of appetite

- Extreme tiredness or unexplained fatigue
- Unintentional weight loss
- Some rare symptoms may include
- Fever
- Pain in bones
- Air bubbles in urine
- Complications

Complications that may result from intestinal cancer are following

Anemia

Iron deficiency may occur as the first symptom of colon cancer.it causes unusual tiredness, shortness of breaths and dizziness [15].

Bowel obstruction

Physical blockage of intestines by tumor results in bowel obstruction which can lead to painful stomach cramps. Solids, liquid and also gases are prevented from passing through the colon.

Jaundice

Another major complication of colon cancer is jaundice, in this condition skin and whites of eyes are masked by yellow color. Jaundice occurs when cancer spreads to the liver.

Risk factors of intestinal cancer

The exact factors causing the intestinal cancer are not well known [16], however some risk factors are strongly linked to the intestinal cancer. Both environmental and genetic factors [17] may contribute to the cause of cancer which includes

- Heavy use of alcohol
- Smoking
- Diet which is high in fats
- Sedentary or inactive lifestyle
- Inherited syndromes

Increasing age (about 90% of intestinal cancer diagnosed after age 50) Mostly the family history has a high risk of developing the cancer.

Intestinal cancer associated with other diseases

Colorectal cancer survivors can face cancer again. Cancer that comes back after Treatment is called Recurrence. But sometimes the recover patient facing unrelated cancer. This is known as second cancer. People who have had colorectal cancer can get any type of second cancer, but they have an increased risk of certain cancer, including (society) [18].

- Uterine
- vaginal cancer
- Stomach cancer
- Lungs cancer
- Small intestine cancer
- Kidney cancer
- **Uterine (vaginal) cancer:** abnormal growth of cells in uterine tissues. Uterine cancer discharge the vaginal which can be foul-smelling, pus and blood tinged (pain during bowel movement). Blood in the stool bleeding from the bladder or rectum. Up to 10% linkage due to hereditary non-polyposis colorectal. It can be diagnosed by Pap test, ultrasound, and biopsy.

- **Stomach cancer:** Is Also known as gastric cancer.it can occur in the abdominal cavity like cancer of colon. (Large intestine), liver, pancreas, small intestine. Because these cancer can have different symptoms and treatments.
- **Lungs cancer:** Intestinal cancer is started from back passage (rectum) or large intestine (colon) and has spread to other parts of body. Due to lungs cancer tiredness and breathlessness caused by a lower than normal level of red blood cell (anemia).
- **Small intestine cancer:** Small intestine is connected with digestive system of human body and having a long tube which is connected with stomach at one's side and at the other side it is connected with large intestine. Small intestinal cancer is rare and it occurs due to eating of high-fat diet.
- **Kidney cancer:** Kidney metastasis is a rare case and may be generally associated with unfavorable prognosis. Colon cancer cleansing product and methodology is very harmful for the proper functioning of kidney that has risk to the kidney. This can cause loss of kidney function and kidney failure.

Management

Although the colorectal cancer have been described, where in the gut a tumor formed for treatment. Usually the single treatment for this stage of colon cancer is the surgical removal, although chemotherapy after surgery may be added. For a stage II rectal cancer, a surgical resection is sometimes preceded or followed by chemotherapy or by radiation [19].

- **Colon surgery:** In colon surgery, structural part of the mesocolon with parietal cavity wall and retro peritoneum should have to be followed for avoiding damage of the ureter, duodenum, pancreas and also spleen. Moreover, mesenteric margins lines are planned precisely, ensuring abundant vascularization of the remnant bowel loops for anastomosis. A torsion-free anastomosis should be created to avoid feared complication of an anastomotic leakage.
- **Rectal cancer:** The standard surgical method used to remove the rectal cancer that lies close to anus is the abdomino perineal operation. Following the APR procedure, the anus is freed with the cancer and cut end of large bowel is the attached to abdominal wall to the form colostomy.
- **Recovery after surgery:** Perioperative protocols like fast track and the better Recovery after Surgery (ERAS) have designed to reduce the surgical complications. The protocol describes the perioperative care pathway and lists elements of the care for these patients at various levels in perioperative process.
- **Metastatic disease:** An overall survival of 30 months has now been achieved in the clinical trials. This improvement in the survival can be attributed to the use of chemotherapeutic and drugs.
- Chemotherapy combinations: The chemotherapy backbone for first-line treatment of metastatic disease is basically a mixture of 5-fluorouracil, leucovorin and oxaliplatin (FOLFOX protocol) and irinotecan (FOLFIRI protocol).
- **Targeted therapies:** Along with combined chemotherapy regimen, targeted agents are used for the metastatic colorectal cancer treatment. Particularly, these may include 3 major group of drugs: monoclonal antibodies against EGFR (cetuximab and panitumumab), second monoclonal antibodies against VEGF-A (bevacizumab), and third one fusion proteins that target multiple proangiogenic growth factors.

Role of Phytochemicals

Grapes: *In vitro* studies have revealed that grapes have these phytochemicals:

- Flavonoids procyanidins, polyphenolic and procayanidin compounds
- Flavonoids and procyanidins: Role in inhibition of proliferation of cancer cells by increasing dihydroceramides p53 and p21 (cell cycle gatekeeper) protein level.
- Grape extracts triggered the antioxidant response by activating the transcriptional factor Nuclear factor erythroid 2-related factor 2 (Nrf2) [20].

Polyphenolic and procayanidin compounds

- Reducing effect on the activity of myeloperoxidase as seen in *in vivo* and *in vitro* studies.
- Another factor that grape seeds can inhibit growth of intestinal cancer by altering the cell cycle which would eventually lead to capase-dependent apoptosis [21].

Soyabeans

saponins

Saponins: Containing saponins which inhibits the activity of the protein kinase C and cyclooxygenase-2 after 72hrs of exposure of cells to it. Also density of the cell decreases [22].

Green Tea leaves

catechin

Catechin: Leaves having high level of catechin increase the level of apopstois in the cancer cell at the same time playing role in reducing expression of Vascular Endothelial Growth Factor (VEGF) [23].

Garlic

- Allicin
- Organosulfurcompounds
- S-allylcysteine
- S-allylmercaptocysteine

Allicin and organosulfur compounds: *In vitro* studies reveal they inhibit growth of cancer cells by promoting apoptosis by inhibition of phosphoinositide 3-kinase/Akt pathway.

Having role in increasing the level of phosphatase and tensin homolog (PTEN)reducing expression of Akt and p-Akt.

S-allylcysteine and S-allylmercaptocysteine: Garlic roots have S-allylcysteine and S-allylmercaptocystein known to exhibit anticancer properties 51 patients whose illness was diagones as intestinal cancer falling in age range of 49- 79 yrs suggest that garlic extracts have an inhibitory effect in the reduction of activity and size of cancer cells.

Olives

Increases peroxidase anions in mitochondria of cancer cells due to presence of maslinic acid 73.35% and oleanolic acid 25.75%. also induces programmed cell death.

Pomegranate fruit

- Punicalagins
- Ellagitannins
- ellagic acid flavonoids (including quercetin, kaempferol, luteolin glycosides) polyphenol compounds (caffeic acids, catechins, saponins, polysaccharides, triterpenoids, alkaloids, glycosides) phenols (quercetin, luteolin, kaemopfrol, luteolin glycosides)

Punicalagins, ellagitannins, ellagic acid, other falvinoids (including quercetin, kaempferol, luteolin glycosides):

Have major roles in anticancer activity by causing reduction of phosphorylation of p65 induced by Akt needed for activity of NFkB [24].

Flavonoids and polyphenol compounds

Effective chemicals after 104 studies are revealed flavonoids, polyphenol compounds such as caffeic acid, catechins, saponins, polysaccharides triterpenoids, alkaloids, glycosides and phenols such as quercetin, luteolin, kaempfrol, luteolin glycosides.

Herbal extracts

They also block specific phase of cell cycle. Extracts from leaves of Annona muricata have role in inhibition of colon cancer cells and induces apoptosis by resting cells at G1 phase.

Further considerations

The role of phytochemicals obtained from different fruits, plants and herbs are proving beneficial for the destruction and removal of cancerous cells. These chemicals play their roles in the blockage of cell cycle at specific phases and their use in further treatment for intestinal cancer will be very beneficial. Patients having symptomatic and more-aggressive metastatic disease without chance of secondary metastatic resection achievement from the active first line treatment to gain optimal tumor controls. Usually be achieved by using double chemotherapy along with the targeted agent such as bevacizumab. For those who are responding to this 'induction' treatment, and who had a stable disease after 4-6 months of treatment, the intensity of the treatment should be minimized to avoid surplus toxicity. Thus, active maintenance, but also treatment discontinuation, can be considered when tumors respond or are stable during a 4-6 months induction treatment and the tumor burden is not very high. In cancers those refractory to 2 lines of chemotherapy, Regorafenib is orally available multikinase inhibitor that has been shown efficacy in patients who had previously been cured with all available therapies in market. Accordingly, it has been become the standard in the already treated patients.

Conclusion

Intestinal cancer, which is common malignancy causes significant numbers of deaths. Although its symptoms are vague, its early and accurate diagnosis is important and is preventable through the screening techniques and nowadays also with the help of different kinds of phytochemicals. Patients with advanced stages of cancer are also seen to be treated with the help of phytochemicals. Further, DNA analysis, preventive diets and healthy lifestyle further reduces the incident of intestinal cancer. The use of phytochemicals in future will prove to be helpful in the fight against intestinal cancer.

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