Cancer Association of South Africa (CANSA)

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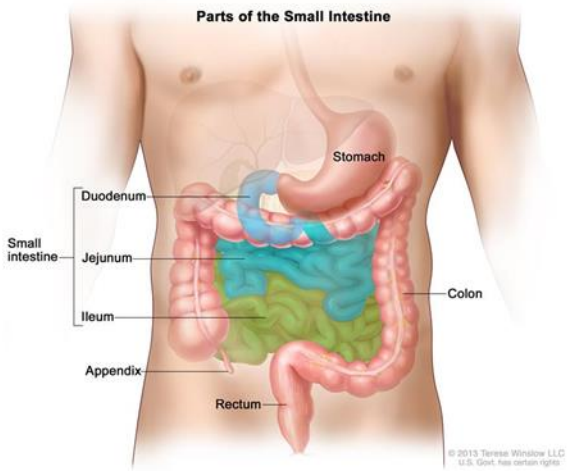
Fact Sheet
on
Cancer of the Small Intestine

Introduction

The small intestine or small bowel is the part of the gastrointestinal tract between the stomach and the large bowel, and is where most of the end absorption of food takes place. It is about 6 metres long.



The small intestine has three distinct regions – the duodenum, jejunum, and ileum.

[**Picture Credit**: Small Intestine}

The shortest region is the **duodenum** which is bout 25.4-cm long. It begins at the pyloric sphincter. Just past the pyloric sphincter, it bends posteriorly behind the peritoneum, becoming retroperitoneal, and then makes a C-shaped curve around the head of the pancreas before ascending anteriorly again to return to the peritoneal cavity and join the jejunum. The duodenum can therefore be subdivided into four segments: the superior, descending, horizontal, and ascending duodenum.

Of particular interest is the hepatopancreatic ampulla (ampulla of Vater). Located in the duodenal wall, the ampulla marks the transition from the anterior portion of the alimentary canal to the mid-region, and is where the bile duct (through which bile passes from the liver) and the main pancreatic duct (through which pancreatic juice passes from the pancreas) join. This ampulla opens into the duodenum at a tiny volcano-shaped structure called the major duodenal papilla. The hepatopancreatic sphincter (sphincter of Oddi) regulates the flow of both bile and pancreatic juice from the ampulla into the duodenum.

The **jejunum** is about 0.9 metres long (in life) and runs from the duodenum to the ileum. Jejunum means “empty” in Latin and supposedly was so named by the ancient Greeks who noticed it was always empty at death. No clear demarcation exists between the jejunum and the final segment of the small intestine, the ileum.

The **ileum** is the longest part of the small intestine, measuring about 1.8 metres in length. It is thicker, more vascular, and has more developed mucosal folds than the jejunum. The ileum joins the cecum, the first portion of the large intestine, at the ileocecal sphincter (or valve). The jejunum and ileum are tethered to the posterior abdominal wall by the mesentery. The large intestine frames these three parts of the small intestine.

Researched and Authored by Prof Michael C Herbst
[D Litt et Phil (Health Studies); D N Ed; M Art et Scien; B A Cur; Dip Occupational Health; Dip Genetic Counselling; Dip Audiometry and Noise Measurement; Diagnostic Radiographer; Medical Ethicist]
Approved by Ms Elize Joubert, Chief Executive Officer [BA Social Work (cum laude); MA Social Work]

Cancer of the Small Intestine
The types of cancer found in the small intestine include:

- Adenocarcinoma - the most common type of small intestine cancer, usually develop in the cells that line the walls of the small intestine. Often, this type of cancer will develop out of small benign (noncancerous) growths called polyps
- Sarcoma - a type of intestinal cancer that develops in the connective tissue of the small intestine
- Leiomyosarcoma (cancer of smooth muscle cells) can develop in the wall of the small intestine. Chemotherapy may slightly lengthen survival time after surgery to remove leiomyosarcomas.
- Kaposi sarcoma is a type of skin cancer that can affect internal organs and sometimes occurs in people with AIDS due to human immunodeficiency virus (HIV) infection. Kaposi sarcoma can occur anywhere in the digestive tract but usually in the stomach, small intestine, or colon. This cancer usually does not cause symptoms in the digestive tract, but bleeding, diarrhoea, and intussusception (one segment of the intestine slides into another, much like the parts of a telescope) may occur. Treatment of Kaposi sarcoma depends on where the cancer is but may include surgery, chemotherapy, and radiation therapy.
- Carcinoid Tumours - form in the lining of the intestines and are often are slow-growing
- Gastrointestinal Stromal Tumour - variants of soft tissue sarcoma.
- Lymphoma - an immune system disease that may originate in the intestines

Tumour Grade and Tumour Stage
Tumour grade and stage are terms used to describe the severity of a tumour, while tumour grade describes the appearance of cancerous cells in the tissue by examining them under a microscope.

Tumour stage encompasses:

- The location of the tumour.
- The size and/or extent of the original tumour.
- Whether cancer cells have spread to lymph nodes or anywhere else in the body.
- The number of tumours present.

Doctors use tumour grade, cancer stage, and a patient's age and general health to decide the course of treatment for the patient and determine prognosis. Prognosis describes all factors including the disease course, cure rate, chances of survival, and risk of recurrence of cancer.

<u>What are the cancer stages?</u>
Different systems of cancer staging are used to describe the types of cancer. Below is a common method in which stages are ranged from 0 to IV.

- Stage 0: The tumour is confined to its place of origin (in situ) and has not spread to nearby tissue.
- Stage I: The tumour is located only in the original organ, is small, and has not spread.
- Stage II: The size of the tumour is large but has not spread.
- Stage III: The tumour has become larger and may have spread to surrounding tissues and/or lymph nodes.
- Stage IV: The tumour has spread to other distant organs of the body, which is known as the metastasis stage.

TNM staging

Another common staging method used for cancer is the TNM system, which stands for tumour, node (which means spread of the tumour to lymph nodes), and metastasis. When a patient's cancer is staged using the TNM system, a number will be present along with the letter. This number signifies the extent of the disease in each category - tumour, node, and metastases.

Another system of cancer staging divides cancer into five stages, which include:

- In situ: Abnormal cells are present but have not spread to nearby tissue.
- Localized: Cancer is located only in the original organ and shows no sign of its spread.
- Regional: Cancer has spread to nearby lymph nodes, tissues, or organs.
- Distant: Cancer has spread to distant parts of the body.
- Unknown: The stage cannot be figured out due to a lack of enough information.

What are the cancer grades?

Cancer grades are based on examination of the suspected tissue sample under a microscope. This involves surgically removing a piece of the suspected cancerous tissue and sending it to the lab for analysis. The entire procedure is known as a biopsy.

A doctor who specializes in diagnostic tests (pathologist) examines the cells of the tissue and determines whether they are harmless (benign or noncancerous) or harmful (malignant or cancerous). They describe the microscopic appearance of the cells and assign a numerical "grade" to most cancers.
Generally, a lower grade indicates slow-growing cancer and a higher grade indicates fast-growing cancer.

The most commonly used grading system is as follows:

- Grade I: Cancer cells that look like normal cells but are not growing rapidly.
- Grade II: Cancer cells that don't look like normal cells with their growth being faster than normal cells.
- Grade III: Cancer cells that look abnormal and have the potential to grow rapidly or spread more aggressively.

Sometimes, the following system can be used:

- GX: Grade cannot be assessed (undetermined grade)
- G1: Well-differentiated (low grade)
- G2: Moderately differentiated (intermediate grade)
- G3: Poorly differentiated (high grade)
- G4: Undifferentiated (high grade)

Incidence of Cancer of the Small Intestine

According to the outdated National Cancer Registry (2017), known for under reprting, the following number of cases of the small intestine cancer was histologically diagnosed in South Africa during 2017. Histologically diagnosed means that a tissue sample (biopsy) was forwarded to an approved pathology laboratory where a specially trained pathologist confirmed a cancer diagnosis:

Group - Males 2017	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All males	81	1:2 206	0,20%
Asian males	6	1:839	0,62%
Black males	31	1:4 843	0,24%
Coloured males	11	1:1 335	0,23%
White males	33	1:1 013	0,15%

Group - Females 2017	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All females	74	1:2 611	0,18%
Asian females	10	1:645	0,78%
Black females	31	1:4 673	0,16%
Coloured females	5	1:3 774	0,11%
White females	28	1:1 185	0,16%

The frequency of histologically diagnosed cases of cancer of the small intestine in South Africa for 2017 was as follows (National Cancer Registry, 2017):

Group - Males 2017	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All males	1	0	7	14	29	16	11	3
Asian males	0	0	0	1	2	1	2	0
Black males	0	0	3	7	16	4	1	0
Coloured males	0	0	1	2	3	4	1	0
White males	0	0	0	1	2	11	8	5

Group - Females 2017	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All females	0	1	4	8	12	23	11	1
Asian females	0	0	0	1	0	3	5	1
Black females	0	1	2	3	6	10	7	2
Coloured females	0	0	0	1	1	2	1	0
White females	0	0	2	3	5	8	8	2

N.B. In the event that the totals in any of the above tables do not tally, this may be the result of uncertainties as to the age, race or sex of the individual. The totals for 'all males' and 'all females', however, always reflect the correct totals.

Risk Factors for Cancer of the Small Intestine

Malignant small intestine tumours occur in a small number relative to the frequency of tumours in other parts of the gastrointestinal tract. There are many suggested reasons for this:

- It has been proposed that the liquid nature of the small intestinal contents may be less irritating to the mucosa, the innermost lining of the small bowel.
- Rapid transit time in the small bowel may reduce exposure of the intestinal wall to cancer-causing agents found in the intestinal contents.
- Other factors that might limit the presence or impact of potential carcinogens (cancer causing agents) include the following:

    - A low bacterial count
    - A large lymphoid tissue component in the wall of the small intestine
    - An alkaline pH inside the small intestine
    - The presence of the enzyme benzpyrene hydroxylase
- Adenocarcinoma of the small bowel is associated with the following underlying conditions:
    - Crohn's disease - An inflammatory disease of the small intestine. Crohn disease usually occurs in the lower part of the small intestine, called the ileum. The inflammation extends deep into the lining of the affected organ, causing pain and making the intestines empty frequently, resulting in diarrhoea.
    - Celiac disease – gluten intolerance
    - Familial polyposis syndromes (FAP) - A group of inherited diseases in which small growths develop in the intestinal tract. In the case of familial adenomatous polyposis, while most polyps and later cancers appear in the large intestine, cancers arising in the small intestine do occur and are often found at the beginning of the small intestine in the duodenum.
- Cancer is more common in the large bowel than in the small bowel. Risk factors in the general population for small intestine cancer include the following:
    - Alcohol consumption
    - Consumption of salted or smoked meats and fish
    - Eating a high fat diet
    - Heavy sugar intake
- Risk factors for developing cancer of the small intestine in Crohn's disease include the following:
    - Male sex
    - Long duration of disease
    - Associated fistulous disease: A fistula is an abnormal connection that passes from one surface to another, such as from the colon to the skin.
    - Surgical removal of part of the bowel
    - The risk of developing small intestinal cancer is 6 times greater for people with Crohn's disease compared to the general population.
- Lymphoma of the small intestine is associated with Celiac disease but is also strongly associated with weakened immune systems such as occurs with HIV/Aids.

Anything that increases ones risk of getting a disease is called a risk factor. Having a risk factor does not mean that one will get cancer; not having risk factors also does not mean that one will not get cancer. Talk with a doctor to find out more about risk.

Wang, N., Yang, J., Lyu, J., Liu, Q., He, H., Liu, J., Li, L., Ren, X. & Li, Z. 2020.
Background: The objective of this study was to develop a practical nomogram for predicting the cancer-specific survival (CSS) of patients with small-intestine adenocarcinoma.
Methods: Patients diagnosed with small-intestine adenocarcinoma between 2010 and 2015 were selected for inclusion in this study from the Surveillance, Epidemiology, and End Results (SEER) database. The selected patients were randomly divided into the training and validation cohorts at a ratio of 7:3. The predictors of CSS were identified by applying both forward and backward stepwise selection methods in a Cox regression model. The performance of the nomogram was measured by the concordance index (C-index), the area under receiver operating characteristic curve (AUC), calibration plots, the net reclassification improvement (NRI), the integrated discrimination improvement (IDI), and decision-curve analysis (DCA).
Results: Multivariate Cox regression indicated that factors including age at diagnosis, sex, marital status, insurance status, histology grade, SEER stage, surgery status, T stage, and N stage were independent covariates associated with CSS. These factors were used to construct a predictive model, which was built and virtualized by a nomogram. The C-index of the constructed nomogram was 0.850. The AUC values indicated that the

established nomogram displayed better discrimination performance than did the seventh edition of the American Joint Committee on Cancer TNM staging system in predicting CSS. The IDI and NRI also showed that the nomogram exhibited superior performance in both the training and validation cohorts. Furthermore, the calibrated nomogram predicted survival rates that closely corresponded to actual survival rates, while the DCA demonstrated the considerable clinical usefulness of the nomogram.
Conclusion: We have constructed a nomogram for predicting the CSS of small-intestine adenocarcinoma patients. This prognostic model may improve the ability of clinicians to predict survival in individual patients and provide them with treatment recommendations.

Cajo, G., Volta, U., Ursini, F., Manfredini, R. & De Giorgio, R. 2019.
BACKGROUND: Small bowel adenocarcinoma (SBA) is a rare neoplasm, which can occur in a sporadic form or can be associated with a number of predisposing conditions such as hereditary syndromes and immune-mediated intestinal disorders, e.g. celiac disease (CD). However, the features of SBA in the context of CD remain only partly understood. This study was aimed to show the main clinical features, diagnostic procedures and management options of SBA cases detected in a large cohort of celiac patients diagnosed in a single tertiary care center.
METHODS: We retrospectively reviewed all the SBA cases detected in a cohort of 770 CD patients (599 females; F / M ratio: 3.5:1; median age at diagnosis 36 years, range 18-80 years), diagnosed at the Celiac Disease Referral Center of our University Hospital (Bologna, Italy) from January 1995 to December 2014.
RESULTS: Five (0.65%) out of our 770 CD patients developed SBA. All of them were female with a mean age of 53 years (range 38-72 years). SBA, diagnosed at the same time of the CD diagnosis in three cases, was localized in the jejunum in four cases and in the duodenum in one case. The clinical presentation of SBA was characterized by intestinal sub-occlusion in two cases, while the predominant manifestation of the remaining three cases was iron deficiency anaemia, abdominal pain and acute intestinal obstruction, respectively. All the patients were referred to surgery, and three cases with advanced stage neoplasia were also treated with chemotherapy. The overall survival rate at 5 years was 80%.
CONCLUSIONS: Although in a limited series, herein presented CD-related SBA cases were characterized by a younger age of onset, a higher prevalence in female gender and a better overall survival compared to sporadic, Crohn- and hereditary syndrome-related SBA.

Barsouk, A., Rawla, P., Barsouk, A. & Thandra, K.C. 2019.
"The latest data from the United States and Europe reveal that rare small intestine cancer is on the rise, with the number of cases having more than doubled over the past 40 years in the developed world. Mortality has grown at a slower pace, thanks to improvements in early diagnosis and treatment, as well as a shift in the etiology of neoplasms affecting the small intestine. Nevertheless, 5-year survival for small intestine adenocarcinomas has lingered at only 35%. Lifestyle in developed nations, including the rise in obesity and physical inactivity, consumption of alcohol, tobacco, and red and processed meats, and occupational exposures may be to blame for the proliferation of this rare cancer. Identification of hereditary and predisposing conditions, likely to blame for some 20% of cases, may help prevent and treat cancers of the small intestine. Studies of the neoplasm have been limited by small sample sizes due to the rarity of the disease, leaving many questions about prevention and treatment yet to be answered."

Signs and Symptoms of Cancer of the Small Intestine
People with small bowel cancer may experience the following symptoms or signs. Sometimes, people with small bowel cancer do not have any of these changes. Or, the cause of a symptom may be a different medical condition that is not cancer.

- Blood in the stool (faeces)
- Dark/black stools

- Diarrhoea
- Nausea and vomiting
- A lump in the abdomen
- Pain or cramps in the abdomen
- Unexplained weight loss
- Low Red Blood Cell count – anaemia
- Yellowing of the skin and eyes - jaundice
- Episodes of abdominal pain that may be accompanied by severe nausea or vomiting

If concerned about any changes experienced, please talk with a doctor. The doctor will ask how long and how often one has been experiencing the symptom(s), in addition to other questions.

Diagnosis of Cancer of the Small Intestine

Small intestine cancer can be difficult to diagnose. A person may have several imaging tests like CT, MRI, X-ray and PET scans. The patient may also have a radioactive substance placed in his/her body for some imaging tests. He/she may also have a test where a long, thin tube with a camera on it is inserted into the body.

If these tests do not find cancer, the patient may need surgery to locate it.

Ocasio Quinones, C.S. & Woolf, A. 2020.

"Small Bowel Cancer encompasses a series of malignant lesions that may be identified throughout the small intestine (SI). The small bowel lies between the stomach and the large intestine (LI/Colon) and is encompassed by three different sections, the duodenum, jejunum, and ileum to the level of the ileocecal valve which provides the terminal transition point between the SI and the LI. While there are both benign and malignant lesions that can be identified throughout the SI, the overall incidence of small bowel neoplasms is extremely low when compared to lesions noted in other portions of the gastrointestinal tract. This article will focus on the overall characteristics, diagnostics, treatment and prognosis of malignant lesions. Majority of these lesions cause multiple non specific symptoms which very often lead to delay in diagnosis and therefore delay in early intervention with available treatment strategies. Common clinical features include abdominal pain, anorexia, gastrointestinal bleeding, and weight loss. More advanced processes can present with perforation, small bowel obstruction, or obstructive jaundice. Diagnosis can be variable based on location of the lesion under investigation and generally consists of laboratory studies, radiographic imaging and endoscopic evaluation. Malignant lesions overall include lymphomas, neuroendocrine tumors (carcinoids), adenocarcinomas and stromal tumors."

Malczewska, A., Witkowska, M., Makulik, K., Bocian, A., Walter, A., Pilch-Kowalczyk, J., Zajęcki, W., Bodei, L., Oberg, K.E. & Kos-Kudła, B. 2019.

INTRODUCTION: Current monoanalyte biomarkers are ineffective in gastroenteropancreatic neuroendocrine tumors (GEP-NETs). NETest, a novel multianalyte signature, provides molecular information relevant to disease biology.

AIM(S): Independently validate NETest to diagnose GEP-NETs and identify progression in a tertiary referral center.

MATERIALS AND METHODS: Cohorts: 67 pancreatic NET (PNETs), 44 small intestine NETs (SINETs), 63 controls. Well-differentiated (WD): PNETs, n=62, SINETs, all (n=44). Disease extent assessment at blood draw: anatomical (n=110)- CT(n=106), MRI(n=7) and/or functional- 68Ga-SSA-PET/CT(n=69) or 18F-FDG-PET/CT (n=8). Image positive disease (IPD) was defined as either CT/MRI or 68Ga-SSA-PET/CT/18F-FDG-PET/CT-

positive. Both CT/MRI and 68Ga-SSA-PET/CT-negative in WD-NETs was considered image negative disease (IND). NETest (normal: 20): PCR (spotted plates).
DATA: mean±SD.
RESULTS: Diagnosis: NETest was significantly increased in NETs (n=111; 26±21) vs. controls (8±4, p<0.0001). 75 (42 PNET, 33 SINET) were image-positive. Eleven (8 PNET, 3 SINET; all WD) were IND. In IPD, NETest was significantly higher (36±22) vs. IND (8±7, p<0.0001). NETest accuracy, sensitivity, specificity: 97%, 99%, 95%. Concordance with imaging: NETest was 92% (101/110) concordant with anatomical imaging, 94% (65/69) with 68Ga-SSA-PET/CT, 96% (65/68) dual modality (CT/MRI and 68Ga-SSA-PET/CT). In 70 CT/MRI-positive, NETest was elevated in all (37±22). In 40 CT/MRI-negative, NETest was normal (11±10) in 31. In 56 68Ga-SSA-PET/CT-positive, NETest was elevated (36±22) in 55. In 13 68Ga-SSA-PET/CT-negative, NETest was normal (9±8) in 10. Disease status: NETest was significantly higher in progressive (61±26; n=11) vs. stable disease (29±14; n=64; p<0.0001) (RECIST 1.1).
CONCLUSION: NETest is an effective diagnostic for PNETs and SINETs. Elevated NETest is as effective as imaging in diagnosis and accurately identifies progression.

Williams, E.A. & Bowman, A.W. 2019.
"Although the small intestine accounts for over 90% of the surface area of the alimentary tract, tumors of the small intestine represent less than 5% of all gastrointestinal tract neoplasms. Common small bowel tumors typically are well evaluated with cross-sectional imaging modalities such as CT and MR, but accurate identification and differentiation can be challenging. Differentiating normal bowel from abnormal tumor depends on imaging modality and the particular technique. While endoscopic evaluation is typically more sensitive for the detection of intraluminal tumors that can be reached, CT and MR, as well as select nuclear medicine studies, remain superior for evaluating extraluminal neoplasms. Understanding the imaging characteristics of typical benign and malignant small bowel tumors is critical, because of overlapping features and associated secondary complications."

Treatment of Cancer of the Small Intestine
Surgery is typically the main treatment for small intestine cancer. For some people, it might be the only treatment they need. At this time, surgery is the only treatment that can cure a cancer of the small intestine.

PDQ Adult Treatment Editorial Board, 2020.
Radical surgical resection.
Surgical bypass of obstructing lesion.
Palliative radiation therapy

Baju, I. & Visser, B.C. 2019.
"Small bowel malignancies are extremely rare. Surgical resection is often the mainstay of treatment with the extent of the operation depending on the type of tumor. Whereas neuroendocrine tumors and adenocarcinoma require lymph node resection, gastrointestinal stromal tumors do not typically metastasize to regional nodes and therefore need resection only. Minimally invasive approaches are applicable to small tumors that require a limited resection and reconstruction and have been shown to have equal survival benefits with decreased risk of postoperative complications."

Obara S, Nakayama H, Kato T, Yamada T, Nakamura Y, Nishimura T, Kito Y, Okamura R. 2019.
"We report the case of a 73-year-old woman with repeated recurrent small intestinal gastrointestinal stromal tumor(GIST) who was referred to our hospital for best supportive care. She underwent surgical resection 4 times and developed recurrent tumors that were resistant to imatinib. She complained of right lower

abdominal pain caused by the recurrent tumor. We performed surgical resection of the tumor and the disseminated tumors synchronously. Histopathological findings of the resected specimen revealed a high-risk GIST. After the operation, she was administered sunitinib(50mg/day)as adjuvant therapy according to a 4-week-on/2-week-off schedule. Due to the resulting adverse effects, the schedule was changed to 1-week-on/1-week-off therapy. She showed no sign of recurrence 38months after the last surgery. Thus, surgical resection and adjuvant molecular targeted therapy may be an effective treatment strategy for recurrent GIST."

About Clinical Trials

Clinical trials are research studies that involve people. They are conducted under controlled conditions. Only about 10% of all drugs started in human clinical trials become an approved drug.

Clinical trials include:

- Trials to test effectiveness of new treatments
- Trials to test new ways of using current treatments
- Tests new interventions that may lower the risk of developing certain types of cancers
- Tests to find new ways of screening for cancer

The South African National Clinical Trials Register provides the public with updated information on clinical trials on human participants being conducted in South Africa. The Register provides information on the purpose of the clinical trial; who can participate, where the trial is located, and contact details.

For additional information, please visit: www.sanctr.gov.za/

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