Expert Views

Borderline Malignancy / Low Malignant Potential Cancers

SCOR
The Art & Science of Risk

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Introduction

Critical Illness (CI) coverage is intended to cover the cost of treating life threatening illnesses like heart attack, strokes or cancer, as these treatments often exceed the amount covered by typical health insurance coverage.

Exactly which diagnosis trigger a CI pay-out, however, differs as they are based on national regulations and specific policy conditions. Coverage eligibilities for cancer, in particular, has been widely debated as its severity and prognosis can differ dramatically by type and stage. Slower spreading and milder forms can often be treated with less invasive, less expensive options and an excellent prognosis. Should these types of cancer still trigger a CI pay-out?

This was the question the Association of British Insurers (ABI) set out to address with their Statement of Best Practice for Critical Illness in 2006. In the statement, the following exclusions were applied to model wording of the cancer definition:

All cancers which are histologically classified as any of the following:

- pre-malignant;
- non-invasive;
- cancer in-situ;
- having either borderline malignancy; or
- having low malignant potential.

In other words, a cancer diagnosis that fit any of the above criteria will not be eligible for a CI coverage. This exclusion was applied because the insurance industry was starting to see claims for fairly manageable conditions, had little to no impact on life expectancy and treatment was mild compared to most of the other cancers we were seeing at that time. As CI protection is intended to cover severe and life-threatening conditions, these less severe forms of cancer were deemed as not fitting the spirit of the policy.

In this report, we will examine the most common types of cancer that are excluded under the ABI's best practices. Although considered relatively rare compared to the likes of lung, breast, prostate and bowel carcinomas, it is important the underwriters and claims professionals are familiar with these conditions and understand the implications of this exclusion.

We hope this report will serve you as a reference guide for assessing Critical Illness (CI) claims for these conditions.

Gastro-Intestinal Stromal Tumour (GIST)

When SCOR issued a research paper on rare cancers in 2009, Gastrointestinal Stromal Tumours (GIST) had been established as a distinct type of cancer for just under 10 years. At the time, approximately 900 patients were being diagnosed each year and that number seems to have remained consistent up until now. Since GISTs do not fit neatly into the typical malignant/benign categories; these cancers can lead to complicated CI cases.

GISTs are very rare soft tissue cancers (Sarcomas) that have a range of behaviours from low to high risk.

- **GI** – Gastrointestinal – Means they can occur anywhere between the oesophagus and rectum
- **S** – Stromal – Refers to the tissue that holds the organ in place (controls movement of the gut)
- **T** – Tumour

Whilst GISTs can occur anywhere within the gastrointestinal tract, 60% occur in the stomach, 30% in the small intestine, 5% in the colon or rectum and 5% in the duodenum. Very few cases are also recorded in the oesophagus, appendix, and other sites.

The exact cause of GISTs remains unknown, although some can be sporadic. There are no apparent lifestyle or environmental issues that have been identified as a cause. That said, we are aware of certain factors that are significant. Like many cancers, it is more prevalent in older ages and is most common among the ages 50 through 80. There are very few diagnoses below age 40.

When GISTs occur in younger ages, they are likely due to an inherited condition called ***primary familial GIST syndrome***. People with this condition are also likely to develop more than one GIST.

Another condition called Neurofibromatosis type 1 (NF1) increases the risk of developing GISTs, amongst other conditions. NF1 is caused by a faulty gene and in half of all cases, the faulty gene is passed from a parent to the child. If either parent has the faulty gene, there is a 50% chance the child will develop NF1. It is also possible for NF1 to develop spontaneously.

People with NF1 often have many tumours that grow along the nerves. They are typically benign, but the presence of these tumours increases the risk of a few other cancers to develop, including GISTs.

Another reason why GISTs may develop in younger ages is due to another inherited condition called ***Carney-Stratakis syndrome***. This is a recently described familial syndrome characterised by GISTs and a type of neuroendocrine tumour called paragangliomas.

In the early stages of the disease, most GIST patients will be asymptomatic. Even when patients develop symptoms later, they can be relatively mild or non-specific. Common symptoms are fatigue, fever, night sweats, abdominal pain, nausea, weight loss, blood in the stools or vomit. These symptoms can be caused by a multitude of problems and so will not necessarily lead a doctor to suspect the diagnosis.

If GIST is suspected, the most common investigation methods will include an endoscopy, endoscopic ultrasound, biopsy, CT/MRI scan and PET scan.

GISTs are usually distinguished from other forms of cancer (including other sarcomas) based on their location and the presence of positive c-KIT (CD117) or PDGFRA membrane cell receptors in the biopsy using immunohistochemistry. They are staged using the traditional TNM classification system which we are familiar with. However, there are other factors which are relevant in assessing the extent of the disease and the mitotic rate is a key tool in assessing the risk. The stage grouping for GIST tumours also depends on where the tumour starts i.e., the gastric or intestinal tracts.

The mitotic rate is a measure of how fast cancer cells are dividing and growing and is eventually described on the pathological report. To find the mitotic rate, the number of cells dividing in a certain amount of cancer tissue is counted. The higher the mitotic rate, the more aggressive the cancer is likely to be. For GISTs, the mitotic rate is either low or high and can be measured in the following:

- Low = Lower than 5/50 High Powered Field
- High = Higher than 5/50 High Powered Field

(One high-power field (HPF) is a standard measure of area, and 50 traditional HPF equals five square millimeters (5 mm^2)).

The stages that are described in Appendix 1 are the most recent classification established by the American Joint Committee on Cancer (AJCC) and have been effective since January 2018.

Historically, GISTs were categorised as being either 'benign' or 'malignant' depending upon the cellular composition of the tumour, with malignant tumours being "high-grade". They have always been described as cancer, being fast growing and with a high risk of metastasising.

The so called 'benign' tumours were described as slow-growing and non-aggressive. However, it is now widely accepted that the terms benign and malignant are not strictly applicable to GISTs as they all are potentially malignant. Instead, tumour size, mitotic rate, primary tumour location, and presence of metastases determine prognosis.

The medical terminology now used for low-grade GISTs is "low malignant potential" with high -grade tumours being considered to be cancer.

Surgery is usually required to remove tumours, even if they are of low malignant potential. The surgery can sometimes be radical depending upon the size and location of the tumour. If there are no current symptoms, the tumour may just be monitored, with surgery and imatinib (Glyvec – a drug that inhibits KIT and PDGFR receptor functions in GIST) only offered if symptoms develop. Once successfully treated, low-grade tumours have an excellent prognosis and are typically associated with a normal life expectancy.

This information is particularly important where CI claims assessors need to consider whether they are excluded due to the borderline malignancy/ low malignant potential wording in use since 2006. If this exclusion applies, the following claims should be declined.

- Stage 1A GISTs that start in the stomach or omentum.
- Stage 1 GISTs of the small intestine, oesophagus, colon, rectum, or peritoneum*.

** Tumours of the peritoneum will be dependent on the quality of the resection (meaning total resection to be sure that the risk of relapse is zero; and because this does not take into account the mitotic rate). In poor prognosis stage I, some patients may be offered imatinib adjuvant therapy which is a pragmatic way of identifying the patients for whom physicians are considering a poor prognosis.*

Declining claims of this nature can be challenging as the claimant will have some expectation of their claim being accepted. Claimants may deserve sympathy if they have been told they have a tumour and have undergone surgery which can be sometimes quite extensive, even though their overall prognosis would be very good in terms of recovery and any future problems.

To address this issue, in recent years insurers have been developing additional payment options that will pay claims at a lower amount for these excluded tumours. SCOR recommends the following wording for such definitions.

Gastrointestinal stromal tumour (GIST) of low malignant potential - with surgery

Gastrointestinal stromal tumour (GIST) of low malignant potential diagnosed by histological confirmation and that has been treated by surgery to remove the tumour.

For the above definition, the following is not covered:

- Tumours treated with radiotherapy, laser therapy, cryptherapy or diathermy treatment

Once a GIST has been diagnosed, the patient will need to commence treatment. As GISTs are very rare, it is preferable that the patient is referred to a specialist centre that is familiar with the disease. The most common type of treatment for GISTs is surgery and removal of the tumour. When additional treatment is required, traditional chemotherapy drugs have not been effective on GISTs. Therefore, targeted therapy drugs such as Imatanib and Sunitinib are used. They can be used either prior to surgery (neoadjuvant) with the aim or reducing the size of a tumour to make it amenable to surgery or following surgery (adjuvant) to attack any residual tumour cells or regrowth. A drug called Regorafenib may be used when Imatanib and Sunitinib cease to be effective.

Claims for lower grade GISTs are notoriously challenging. Therefore, the histology is essential and the input of a CMO is advisable. If the case is discussed with a CMO, it is imperative that any applicable exclusions and/or additional benefit definitions are brought to their attention so that they can be considered.

Neuroendocrine Neoplasms (NENs)

Neuroendocrine cells are present throughout the body. They create a network to keep us well by monitoring what is happening within the body and communicate with each other to release specific substances such as gut hormones to help the body function normally. Cancers of these cells, however, have been historically misunderstood. Our understanding of these cancers continues to evolve.

In the research paper on rare cancers issued in 2009, there was a chapter on Carcinoid Tumours. However, the terminology for these tumours has changed several times in the past decade. The original term, "Carcinoid", was replaced by neuroendocrine neoplasm (NEN). It is also sometimes referred to as neuroendocrine tumours (NET). The NEN classification also includes neuroendocrine carcinoma's (NEC). NETs are further considered on their degree of malignancy and can range from indolent to very aggressive and prognosis depends on the differentiation and proliferation rates (Ki-67 (MIB) or mitotic rate). However, NECs are always associated with poor prognosis.

Although still considered relatively rare, the incidence of NENs is now considered significantly higher than it was a decade ago. In 2009, it was estimated that approximately 1,200 people were diagnosed each year in the UK. Today, over 4,000 people are diagnosed with a NEN each year in the UK, and they are becoming more common across the globe. This might be because there are better tests to diagnose them. In addition, improved disease coding and data collection are likely to be a factor contributing to the apparent increase in prevalence.

The term Neuroendocrine Tumour has been used as an umbrella term to describe cancer of the Neuroendocrine System.

NET was first described as a specific disease as far back as the mid-1800's. In the early 1900's, the term 'Carcinoid' began to be used. This term became very popular amongst the medical community at the time, as it was believed that NETs behaved very differently than common cancers.

It was thought that all NETs were very indolent and less likely to spread or behave in the same way as other malignancies. However, in the 1950's it revealed that some 'Carcinoids' could behave in a more malignant fashion and could spread to other parts of the body, and, in some cases, be quite aggressive.

Nowadays, most medical publications refer to them as Neuroendocrine Neoplasms (NEN).

The term NEN was primarily introduced to help distinguish between the two specific types of Neuroendocrine Cancer: NET and NEC. NETs have a particular appearance under the microscope as they are 'well-differentiated'. In NECs, these changes are said to be 'poorly differentiated' and are likely to be more aggressive.

In addition to this, NENs are described as 'functional' or 'non-functional'. Most NENs (60%) are non-functional, meaning there are no endocrine symptoms associated, and they will therefore be discovered at advanced, often inoperable, stages. Functional NENs make and release hormones and other substances into the body, which in turn cause symptoms. Carcinoid syndrome is a sign of a functional NEN, in which a substance called serotonin is released. This can cause diarrhoea and facial flushing.

The hormones produced by the neuroendocrine cells will depend on what part of the body they are in. Examples will include the following:

- **Digestive system** – Hormones are produced to help break down food in the gut and move food through the small and large bowel, helping both nutritional uptake and eliminating waste.
- **Respiratory system** – Hormones are produced to help with the development of the lungs and to regulate breathing.
- **Brain** – Hormones are produced to help with

breastfeeding, social bonding, and sleep/wake pattern.

- **Adrenal glands** – Hormones are produced to help control blood pressure and heart rate, amongst other things.

With such a widespread and varied distribution, cancer of the Neuroendocrine system can result in several different symptoms and is dependent on which neuroendocrine cells are affected.

The medical profession currently does not have universal staging criteria for these types of tumours. However, the grading system noted below, using mitotic rate and Ki-67 index can be used as a guide to describe the aggressiveness of these tumours.

The mitotic rate is also a key consideration, and this has been described in the GIST section.

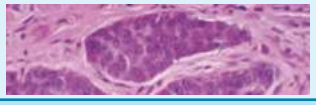
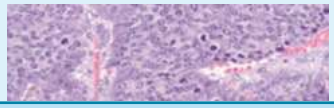
In low-grade cancer, the relatively small percentage of cells dividing means that tumours grow slowly, which is one of the reasons it can take years to develop and be diagnosed. It also likely explains why many people remain asymptomatic.

Higher grade Neuroendocrine cancers often grow more rapidly and can behave more like the more common malignancies. The highest-grade are the NECs.

NENs of the GI tract and pancreas have their own staging systems based on the location and characteristics of the tumour. Some NENs use the TNM staging system used for other cancers. For example, the staging of a lung NEN is the same as the staging of non-small cell lung cancer.

These various stages are documented in Appendix 2.

For a number of years now, claims for NETs have been quite problematic. As described earlier, since 2006 the cancer definition has excluded cancers that are described as having either borderline malignancy or having low malignant potential.

	Well-differentiated NET (Low grade, G1)	**Well-differentiated NET (Intermediate grade, G2)**	**Poorly differentiated NEC (High grade, G3)**
			
Appearance	Monomorphic population of small, round cells		Cellular pleomorphism
Prognosis	Prolonged survival	intermediate	poor
Mitotic rate	<2 mitoses/10 HPF	1-20 mitoses/10 HPF	>20 mitoses/10 HPF
Ki-67 index	<3%	3%-20%	>20%

- Grade 1 = Ki-67* index is less than 3% i.e. fewer than 3% of tumour cells are actively dividing (Well-differentiated)
- Grade 2 = Ki-67 index is between 3% and 20% (Well-differentiated)
- Grade 3 = Ki-67 index is more than 20% (Poorly differentiated)

**Ki-67 is a protein that is present during all the active stages of the cell cycle, making it a useful marker of cell division and growth. For NENs, it is highly likely you will see Ki-67 and mitotic rate referenced in histology reports. They are the measurements used to assess the rate at which a cancer is growing.*

Many NETs have either a very low mitotic count or low Ki-67 index, and as such, were described as having 'low malignant potential'. Low-grade NETs have an excellent prognosis and there was little to no impact on a person's life expectancy and so were not in keeping with what a CI product was designed to cover. Therefore, claims that were low-grade were being declined and the exclusion invoked.

Much like with GISTs, as the number of claims being declined began to increase, the industry started to develop additional payment definitions that would pay a set amount for the claims that were being declined. At the time this was typically up to £25,000 or 25% of the full sum assured.

A typical definition in use is as follows:

Neuroendocrine tumour (NET) of low malignant potential - with surgery

Neuroendocrine tumour (NET) of low malignant potential diagnosed by histological confirmation and that has ben treated by surgery to remove the tumour

For the above definition, the following is not covered:

- Tumours treated with radiotherapy, laser therapy, cryptherapy or diathermy treatment

Despite the additional payment criteria, the industry started seeing challenges for claims where the full benefit was not being paid. The main issue we faced was that the medical profession did not have universal staging criteria for these types of tumours. Given the lack of consistency, some doctors agreed the exclusion should apply, whereas others felt that the full cancer definition was met. Given the lack of consistency, a pathologist could still argue a Grade 1 (G1) NEN, low Ki-67 index has still invaded adjacent cells and therefore would not fit into the current wording.

Given the issues experienced by the industry for both NETs and GISTs, the ABI has looked to address this in the latest Minimum Standards revisions released in September 2022. Going forward, the following exclusion is in the ABI model wording within the cancer definition:

Gastrointestinal stromal tumours and neuroendocrine tumours without lymph node involvement or distant metastases unless they are WHO Grade 2 or above.

This new wording seeks to add clarity to the exclusion by stipulating a minimum of WHO grade 2, which indicates tumours of at least intermediate grade. This would further indicate there is some mitotic activity and/or a Ki-67 index of at least 3% to qualify for benefit. Therefore, claims where the disease is of at least moderate severity, will continue to be paid, but low-grade disease will be declined or qualify under the additional payment criteria.

Treatment

As with most cancers, treatment options may consist of surgery, somatostatin analogues, targeted therapy (everolimus and sunitinib), chemotherapy, external radiotherapy, and interferon therapy. However, other treatment options are available.

Particular attention is currently made on various forms of targeted peptide receptor radiotherapy (PRRT) that can be referred as an internal radiation therapy. This form of systemic treatment combines peptide that target membrane receptors of cancer cells with high affinity and are loaded with radionucleotides that deliver radiation directly at the contact of cancer cells. The radioactive nucleotides circulate throughout the body in the bloodstream and the tumour cells pick up the radioactive material wherever they are in the body, eventually killing NEN cells. Currently available PRRTs are Yttrium 90-DOTATOC, lutetium 177-DOTATE, and 131MIBG.

The off-target delivery of radioactive material is associated with side effects and suspected to be associated with long-term myelodysplastic syndromes including leukaemia.

In addition, other treatments may be offered to help control the symptoms caused by NENs. Somatostatin analogues and Ocreotide injections

are given to help slow down the production of hormones which cause the symptoms associated with carcinoid syndrome.

Targeted drugs are likely to be used for more aggressive tumours that have already metastasised and are not amenable to surgery or when other treatments have stopped responding.

Hepatic artery embolisation is used when metastases are predominantly present in the liver. The treatment aims to stop or reduce the blood supply to the liver as tumours cannot survive without it. This is occasionally combined with chemotherapy.

Pseudomyxoma Peritonei (PMP)

PMP is a very rare type of cancer. The incidence of PMP is believed to be approximately 1-3 out of a million per year. It is often an incidental finding, and most patients are diagnosed during, or after a laparotomy or laparoscopy for suspected appendicitis, peritonitis or gynaecological cancer. It most commonly presents in the appendix but can also occur in the bowel, ovary, and bladder.

It usually begins as a small polyp which can eventually spread through the wall of the site of origin. Eventually the polyp perforates, which often results in a slow leak of mucus leading to the spread of cancerous cells to the lining of the abdominal cavity (the peritoneum). These cancerous cells produce mucus, which collects in the abdomen as a jelly-like fluid called mucin.

Doctors often call PMP a borderline malignancy. However, it is apparent that there is a spectrum varying from slowly progressive to aggressively malignant. Malignant cancers we are familiar with tend to spread to other parts of the body through the lymphatic and circulatory systems. However, PMP doesn't behave in the same fashion, and it doesn't spread to distant sites although it can spread throughout the peritoneum (a serous membrane forming the lining of the abdominal cavity).

The mechanism of the peritoneal cavity involves the production, circulation, and absorption of peritoneal fluid. The tumour cells have little to no adhesive properties and so are unable to attach themselves to any structures. Therefore, they accumulate within the peritoneal fluid.

When a polyp arises within the appendix, as it grows it can occlude the lumen. This can be classified as a low-grade appendiceal mucinous neoplasm (LAMN). If the diagnosis is made before the appendix ruptures and the mucin created is contained within the appendix, this is termed a LAMN-1 lesion. This is unlikely to require any additional treatment once the appendix has been removed. SCOR would suggest that the borderline malignancy exclusion is invoked to decline CI claims of this nature.

If the appendix ruptures, mucus containing epithelial cells can leak into the peritoneal cavity, leading to low-grade mucinous carcinoma peritonei. This is termed a LAMN-2 lesion.

LAMN-2 can be trickier than LAMN-1 as the treatment options can vary. Some patients may only require a watch and wait approach. However, surgery and chemotherapy are also an option

which can be quite extensive. Most LAMN-2 have already spread to the peritoneum, are not curable and will undergo multiple recurrences that will strongly affect the quality of life and potentially reduce life expectancy. We would suggest that these cases are referred to a CMO for consideration.

PMP occurs when the tumour has caused rupture of the appendix with widespread dissemination of mucin throughout the peritoneal cavity. As with most cancers, the primary aim of treatment is total resection of the tumour. Surgery remains the standard of care but often fails to remove the multiple, often microscopic, deposits spread in the peritoneal cavity. Treatment options beyond surgery are limited as chemotherapy has very limited effects and radiation therapy is not possible. Therefore, complete cytoreductive surgery (CRS) is often combined with hyperthermic intraperitoneal chemotherapy (HIPEC).

HIPEC is a highly concentrated and heated chemotherapy treatment delivered directly to the abdomen during CRS. Unlike systemic chemotherapy delivery, which circulates throughout the body via the bloodstream, HIPEC delivers chemotherapy directly to cancer cells in the abdomen. This allows for higher doses of chemotherapy treatment. Heating the solution also tends to improve the absorption of chemotherapy drugs by tumours and destroy microscopic cancer cells that remain in the abdomen after surgery. When as much tissue as possible has been removed, a heated, sterilised chemotherapy solution is delivered to the abdomen to penetrate and destroy any remaining cancer cells. It is circulated throughout the abdomen for approximately 90 minutes and then drained before the incision is closed. This is a very complex and major procedure that can take up to nine hours.

In summary, although it is often termed as a borderline malignancy, due to the severity of the disease and treatment required, SCOR would support payment of claims for PMP under a standard cancer definition. In fact, some insurers have now begun to specifically state that it is covered within their full cancer definition.

Summary

The cancers described in this paper are extremely rare and this is confirmed by their low incidence both nationally and globally. However, in some cases, their numbers do appear to be on the rise. This may be due to better awareness and better understanding of these cancers, as well as updates to disease coding and improving data collection methods.

From an insurer's point of view, considering these cancers at such a granular level and taking the time to understand the risks and prognosis based on sub-categorisation by site of origin (i.e., appendix, bowel, stomach, etc.) is a new approach. While this approach allows us to better understand these cancers on a case-by-case basis, it also means that it is difficult for us to compare the rate of claims we have seen historically with the rate we are seeing now.

We hope this report will serve as a reference guide for assessing CI claims for these rare but potentially serious conditions.

For the cancers discussed in this report, SCOR strongly advocates obtaining histology reports when collecting evidence. It is also advisable to obtain the hospital reports as they are likely to add extra details in the claimant's history, initial presentation and investigations, which help build a picture.

For all claims that are outside the norm, a CMO opinion should always be sought to ensure the correct decision is being made. SCOR has a panel of CMOs including Professor James Brenton, who is a Consultant Medical Oncologist working at the Addenbrookes Hospital Cancer Research UK Cambridge Research Institute (one of the specialist centres for treatment of GIST's), and Professor

Eric Raymond MD, PhD, who is a board-certified medical oncologist and Professor of medical oncology at the University of Paris, France. We would be happy to refer cases to them, if required.

SCOR Oncologist, Professor Raymond

The definition of cancer has been extending over the last few decades based on a better understanding of tumour biology. As such, some which were initially thought benign tumours, but at the fringe of malignancy, are now reclassified as 'borderline malignant' based on their potential of recurrence and developing metastases. Most of those borderline tumours usually have a better prognosis than classical malignancies, but not all of them will remain indolent and many will sooner or later behave like full potential malignancies. Medically, establishing the prognosis of an individual is based on multiple clinical, biological and molecular factors that are usually in the hands of a few medical experts in each country.

As a result, navigating the complexity of those borderline tumours is quite challenging as definitions, classifications, and prognostic factors don't always look like the 'classical' parameters used in most frequent tumour types. As part of the gastrointestinal tumour board in my institution on a daily basis, I am involved in the care of patients with neuroendocrine tumours, GISTs, and peritoneal pseudomyxomas for which diagnosis and medical care have been dramatically improving over the last 20 years, allowing the people suffering from those diseases to live longer and in better health. Long-term survivors applying for insurance or making claims for Critical Illness often generate many questions; for which medical expertise may be required. Having read and contributed to this paper, I would like to thank Paul Blyth, SCOR's Underwriting and Claims Proposition Manager for taking over the challenge of focusing on those rare diseases, which eventually allows a better understanding of the natural history of borderline malignancies.

SCOR commentary

In recent years, Critical Illness products have been developed to offer additional payments at the reduced sum assured levels for GISTs and NETs, which appears to indicate that CI policyholders with these conditions should receive some form of payment but that they were not intended to be included under the main Critical Illness Cancer benefit.

However, there has been recent debate in the UK about whether the terms 'borderline malignancy' and 'low malignant potential' as sometimes used to describe these tumours, are fit for purpose as they often do not reflect the associated risk and severity. Following a review of the UK Critical Illness minimum standards document, there appears to be broad support in the industry for the recommendation to exclude GISTs and NETs from the full sum assured benefit and this is reflected in the latest model wording which has just been issued by the ABI. SCOR will continue to proactively monitor our philosophy for these conditions and reflect any changes to SOLEM, our underwriting and claims manual.

Appendix 1

Below are the various staging tables for gastrointestinal stromal tumours, depending on the site of origin.

GISTs that start in the stomach or omentum			
AJCC stage	**Stage Grouping**	**Mitotic Rate**	**Stage Description**
1A	T1 or T2 N0 M0	Low	The cancer is: • 2cm (4/5 of an inch) or less (T1) OR • larger than 2cm but not more than 5cm (2 inches) (T2). It has not spread to nearby lymph nodes (N0) or to distant sites (M0). The mitotic rate is low.
1B	T3 N0 M0	Low	The cancer is larger than 5cm (2 inches) but no more than 10cm (T3). It has not spread to nearby lymph nodes (N0) or to distant sites (M0). The mitotic rate is low.
2	T1 N0 M0	High	The cancer is 2cm or smaller (T1). It has not spread to nearby lymph nodes (N0) or to distant sites (M0). The mitotic rate is high.
			OR
	T2 N0 M0	High	The cancer is larger than 5cm (2 inches) but no more than 10cm (T3). It has not spread to nearby lymph nodes (N0) or to distant sites (M0). The mitotic rate is high.
			OR
	T4 N0 M0		The cancer is larger than 10cm (T4). It has not spread to nearby lymph nodes (N0) or to distant sites (M0). The mitotic rate is low.
3A	T3 N0 M0	High	The cancer is larger than 5cm (2 inches) but not more than 10cm (T3). It has not spread to nearby lymph nodes (N0) or to distant sites (M0). The mitotic rate is high.
3B	T4 N0 M0	High	The cancer is larger than 10cm (T4). It has not spread to nearby lymph nodes (N0) or to distant sites (M0). The mitotic rate is high

4	Any T N1 M0	Any rate	The cancer is any size (Any T) AND it has spread to nearby lymph nodes (N1). It has not spread to distant sites (M0). The cancer can have any mitotic rate.
		OR	
	Any T Any N M1	Any rate	The cancer is any size (Any T) AND it might or might not have spread to nearby lymph nodes (Any N). It has spread to distant sites such as the liver (M1). The cancer can have any mitotic rate.

GISTs of the small intestine, oesophagus, colon, rectum, or peritoneum			
AJCC stage	**Stage Grouping**	**Mitotic Rate**	**Stage Description**
1	T1 or T2 N0 M0	Low	The cancer is: * 2cm (4/5 of an inch) or less (T1) OR * larger than 2cm but not more than 5cm (2 inches) (T2). It has not spread to nearby lymph nodes (N0) or to distant sites (M0). The mitotic rate is low.
2	T3 N0 M0	Low	The cancer is larger than 5cm (2 inches) but no more than 10cm (T3). It has not spread to nearby lymph nodes (N0) or to distant sites (M0). The mitotic rate is low.
3A	T1 N0 M0	High	The cancer is 2cm or smaller (T1). It has not spread to nearby lymph nodes (N0) or to distant sites (M0). The mitotic rate is high.
		OR	
	T4 N0 M0	Low	The cancer is larger than 10cm (T4). It has not spread to nearby lymph nodes (N0) or to distant sites (M0). The mitotic rate is low.

3B	T2 N0 M0	High	The cancer is larger than 2cm but not more than 5cm (T2). It has not spread to nearby lymph nodes (N0) or to distant sites (M0). The mitotic rate is high
			OR
	T3 N0 M0	High	The cancer is larger than 5cm (2 inches) but not more than 10cm (T3). It has not spread to nearby lymph nodes (N0) or to distant sites (M0). The mitotic rate is high.
	T4 N0 M0	High	The cancer is larger than 10cm (T4). It has not spread to nearby lymph nodes (N0) or to distant sites (M0). The mitotic rate is high
4	Any T N1 M0	Any rate	The cancer is any size (Any T) AND it has spread to nearby lymph nodes (N1). It has not spread to distant sites (M0). The cancer can have any mitotic rate.
			OR
	Any T Any N M1	Any rate	The cancer is any size (Any T) AND it might or might not have spread to nearby lymph nodes (Any N). It has spread to distant sites such as the liver (M1). The cancer can have any mitotic rate.

Appendix 2

Below are the various staging tables for Neuroendocrine Neoplasms depending on the site of origin.

Stomach			
T1	The tumour is 1 cm or smaller and has grown into a deeper layer of cells in the stomach, the lamina propria or submucosa.	Stage I	There is a small tumour, and it has not spread elsewhere (T1, N0, M0).
T2	The tumour is larger than 1 cm in size, or it has grown into the muscle layer of the stomach, called the muscularis propria.	Stage II	The tumour is larger and has grown as far as the subserosa, which is behind the layer of muscle in the stomach. The cancer has not spread to the lymph nodes or elsewhere in the body (T2 or T3, N0, M0).
T3	The tumour has grown through the muscularis propria and into the subserosa layer behind it.	Stage III	The tumour is any size, and the cancer has spread to regional lymph nodes (any T, N1, M0). Or, the tumour has spread to the outside of the stomach, but the cancer has not spread to the lymph nodes or elsewhere (T4, N0, M0).
T4	The tumour has grown into the layer of tissue on the outside of the stomach, called the serosa or peritoneum, or it has spread into nearby organs or structures.	Stage IV	There is distant metastasis (any T, any N, M1).

Duodenum and ampulla of Vater (small intestine)			
T1	The tumour is 1 cm or smaller and only involves the top layer of mucus membrane or connective tissue on top of the muscle layer of the duodenum or it only involves the sphincter of Oddi. The sphincter of Oddi is a muscle that controls the flow of digestive juices into the duodenum through the ampulla of Vater.	Stage I	There is a small tumour, and it has not spread elsewhere (T1, N0, M0).
T2	The tumour is larger than 1 cm in size. Or it has grown into the muscle layer of the duodenum, called the muscularis propria, or through the sphincter of Oddi and into the duodenum.	Stage II	The tumour is larger than 1 cm, or it has grown as far as the pancreas. The cancer has not spread to the lymph nodes or elsewhere in the body (T2 or T3, N0, M0).
T3	The tumour has grown into the pancreas or the tissue surrounding the pancreas.	Stage III	The tumour is any size, and the cancer has spread to regional lymph nodes (any T, N1, M0). Or, the tumour has spread to the peritoneum or other organs, but the cancer has not spread to the lymph nodes or elsewhere (T4, N0, M0).
T4	The tumour has grown into the peritoneum or other organs.	Stage IV	There is distant metastasis (any T, any N, M1).

Jejunum and ileum (small intestine)			
T1	The tumour is 1 cm or smaller and only involves the top layers of tissue in the small intestine.	Stage I	There is a small tumour, and it has not spread elsewhere (T1, N0, M0).
T2	The tumour is larger than 1 cm in size, or it has grown into the muscle layer of the small intestine.	Stage II	The tumour is larger than 1 cm, or it has grown as far as the pancreas. The cancer has not spread to the lymph nodes or elsewhere in the body (T2 or T3, N0, M0).
T3	The tumour has grown through the muscle layer and into the tissues beyond, but it has not grown outside of the small intestine.	Stage III	The tumour is any size, and the cancer has spread to regional lymph nodes (any T, N1, M0). Or, the tumour has spread to the peritoneum or other organs, but the cancer has not spread to the lymph nodes or elsewhere (T4, N0, M0).
T4	The tumour has grown past the outside of the small intestine and into the peritoneum or other organs.	Stage IV	There is distant metastasis (any T, any N, M1).

Appendix			
T1	The tumour is 2 cm or smaller.	Stage I	There is a tumour of 2 cm or less, and it has not spread elsewhere (T1, N0, M0).
T2	The tumour is more than 2 cm but less than or equal to 4 cm in size.	Stage II	The tumour is larger than 2 cm and has grown as far as the membrane that connects the appendix to the abdomen wall. The cancer has not spread to the lymph nodes or elsewhere in the body (T2 or T3, N0, M0).
T3	The tumour is larger than 4 cm, or it has grown into the layers of tissue on the outside of the appendix.	Stage III	The tumour is any size, and the cancer has spread to regional lymph nodes (any T, N1, M0). Or, the tumour has spread to the peritoneum or beyond, but the cancer has not spread to the lymph nodes or elsewhere (T4, N0, M0).
T4	The tumour has grown through the peritoneum or has invaded nearby organs or structures.	Stage IV	There is distant metastasis (any T, any N, M1).

Colon and Rectum			
T1	The tumour is 2 cm or smaller and has grown past the top layer of cells and into the layers beneath, such as the lamina propria or submucosa. * T1a = The tumour is <1cm in size * T1b = The tumour is between 1cm and 2cm in size	Stage I	There is a tumour of 2 cm or less, and it has not spread elsewhere (T1, N0, M0).
T2	The tumour has grown into the muscle (muscularis propria). Or it is more than 2 cm in size and has invaded the lamina propria or submucosa.	Stage II	The tumour is larger than 2 cm and has grown as far as the membrane that connects the appendix to the abdomen wall. The cancer has not spread to the lymph nodes or elsewhere in the body (T2 or T3, N0, M0).
T3	The tumour has spread through the muscle and into the subserosal tissue behind it.	Stage III	The tumour is any size, and the cancer has spread to regional lymph nodes (any T, N1, M0). Or, the tumour has spread to the peritoneum or beyond, but the cancer has not spread to the lymph nodes or elsewhere (T4, N0, M0).
T4	The tumour has spread to the peritoneum or has invaded nearby organs or structures.	Stage IV	There is distant metastasis (any T, any N, M1).

This article is written by:

Paul BLYTH
Underwriting and Claims Proposition Manager
pblyth@scor.com

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