Understanding Your Pathology Report: Colon Cancer

What is a pathology report?

A pathologist is a doctor who specializes in diagnosing diseases by examining tissue from the body. You will probably never meet the pathologist, but samples of your colon tissue, removed during surgery or biopsy, will be sent to them for review. The pathologist prepares a report of their findings, which is called the pathology report. This report contains important information about the tumor that is used to make treatment decisions. You should request a copy of this report and keep it in your personal files.

What will you find on a pathology report?

The report is broken down into a few sections, including some information about the patient, diagnosis (if known), procedure, a description of what the specimen looks like to the naked eye (called gross description), a description of what was seen under the microscope (microscopic description), and a diagnosis. In the case of a colon cancer, the pathologist will describe the type of cell the cancer comes from, how deeply the tumor goes into the colon wall, the histologic grade of the tumor, if there is vascular invasion and if any lymph nodes are involved. To help you read your report, let's go through each of these sections individually.

The Gross Description

This is generally not that important to the patient. It is a description of the sample the pathologist received and what they see with the naked eye. In a biopsy, the specimen is likely a small, nondescript piece of tissue, in which case the pathologist may describe the color, shape, feeling and size of the tissue. After a cancer surgery, multiple organs or tissues may be submitted and described in the report. This might include size, color and weight. For example, a colon specimen from a colectomy may be described as:

"Specimen #1 is labeled "colon" and consists of a segment of bowel measuring 13cm in length after fixation. The specimen is surrounded by a moderate amount of pericolonic fat. 3cm from one resection margin is an ulcerated round tumor measuring 3.2cm in diameter. The rest of the mucosa is grossly unremarkable."

This tells us the specimen was a 13cm long piece of colon, with a tumor located 3cm from one end. This isn't very helpful in determining stage or treatment, so let's move on to the next section.

Microscopic Diagnosis

This section may be called microscopic diagnosis or just diagnosis. This is the meat of the report, but we need to understand a bit about the colon in order to understand this part of the report. The colon, or large intestine, is a tube that is about 5 to 6 feet in length; the first 5 feet make up the colon, which then connects to about 6 inches of rectum, and finally ends with the anus. The colon is made up of several sections and your report may specify which section the tumor was located in. These sections are called the cecum, ascending, transverse, descending and sigmoid colons, rectum and anus (see diagram). The splenic and hepatic flexures are areas where the colon bends (or flexes) that are named for the organs they are located near.

The colon, which is shaped like a tube, is made up of several layers, starting with the innermost layer, the mucosa (which is made up of epithelium), and then the lamina propria and muscularis mucosa. This is surrounded by the submucosa, which is surrounded by two layers of muscle (or muscularis), and finally, the serosa layer, which is the outside layer of the tube. The outside of the colon is covered with a layer of fat, also called adipose tissue, which contains lymph nodes and blood vessels which feed the colon tissue.
Now that we understand a bit about the anatomy of the colon, let's go through the things you might see in this section of the report.

**Tumor Cell Type**

The type of colon tumor describes the cells from which the tumor arises. Adenocarcinoma is the most common type, accounting for 95-98% of colon cancers. An adenocarcinoma arises from the glandular cells that line the inside of the colon. Two subtypes of adenocarcinoma are signet ring and mucinous, which are both named for the way the cells look under the microscope. The other 2-5% of cancers found in the colon are lymphomas, gastrointestinal stromal tumors (GIST), and carcinoid tumors, which will not be discussed in this article.

If a polyp was removed, this section will describe the type of polyp. A colon polyp is a benign growth that, over time, can turn into cancer. For that reason, they are removed during a colonoscopy and may be sent to the pathologist to determine what type of polyp it is. There are several types of polyps that can be found in the colon:

- **Tubular adenoma (also called adenomatous polyp):** this accounts for 70% of the polyps found in the colon and can progress into cancer, but this happens over many years. If they are found early, they can be removed during colonoscopy.
- **Villous adenoma:** this accounts for 15% of the polyps found in the colon. This type of polyp has the highest risk of turning into cancer. In some cases these can be removed during colonoscopy, but in other cases surgery is required.
- **Hyperplastic polyps and Inflammatory (or pseudopolyps):** these two types of polyps are not likely to turn into a cancer.

In addition, colon polyps come in two forms, called pedunculated and sessile. Pedunculated polyps grow on a stalk and look like a small mushroom, which can usually be easily removed during a colonoscopy. The sessile type of polyp is flat and grows on the wall of the colon. These are much more difficult to remove and may require surgery to remove the entire polyp.

**Histologic Grade**

As normal cells develop, they "differentiate" to become a specific type of cell. Histologic grade describes how closely the tumor cells resemble normal cells. The more a tumor cell looks like a normal cell, the more well-differentiated it is. On the other hand, the more cells do not look like normal cells (higher grade) the more aggressive they are, growing and spreading faster.

Histologic tumor grade is broken down as follows:

**Tumor Grade (G)**

- **GX:** The tumor grade cannot be identified.
- **G 1:** also called well differentiated. Cells appear the most normal.
- **G 2:** also called moderately differentiated. Cells appear somewhat like normal cells.
- **G 3:** also called poorly differentiated. Cells look less like normal cells.
• G4: also called undifferentiated. Cells appear the most abnormal and barely look like normal cells.

Depth of Invasion

A tumor that has not invaded the surrounding tissues is sometimes called "in situ", while tumors that have penetrated surrounding tissues are called invasive. The diagnosis section will include information on the layers of the colon that the tumor has invaded (the depth of invasion) and if it has extended beyond the colon into surrounding tissue. Some examples include:

• "The biopsy shows involvement of the mucosal lamina propria by neoplastic glands. The submucosa is not involved." This tumor invades only the innermost layer of the colon.
• "The tumor invades through the muscularis propria but not into the pericolonic adipose tissue. The serosal surface is not involved." This tumor invades the muscle layer, but does not invade the serosa (the outer layer of the colon) or the surrounding fat.
• "The tumor is invasive through the muscularis propria into the pericolonic fat." This tumor has penetrated through the colon wall and into the surrounding fat.

Lymphovascular Invasion

When the pathologist examines the tumor and surrounding tissue available to them, they look at the tiny blood vessels and lymphatic drainage to see if any tumor cells have invaded them. This is different from the lymph nodes and would be reported as whether or not lymphovascular invasion is seen. The presence of this may be a sign of a more aggressive tumor.

Lymph Nodes

The lymph system is essentially the "housekeeping system" of the body. It is a network of vessels (tubes) which connect lymph nodes. These nodes can vary in size, but are normally up to about 2 centimeters in width. They contain cells that clear bacteria and other foreign debris from the body. Lymph is a watery liquid that flows between cells in the body, picking up foreign debris and taking it into the lymph node for filtering and ultimately, elimination by the liver.

Cancer cells use the lymph system as a first step to traveling to other areas of the body. During a colon cancer surgery, numerous lymph nodes are removed and checked for the presence of cancer cells. This will be reported as the number of lymph nodes that contained cancer cells and how many were examined. For example, the report might state "fifteen benign lymph nodes (0/15)" or "tumor seen in sixteen of twenty lymph nodes (16/20)."

In a colon cancer surgery, the more lymph nodes removed the more certain you can be that no lymph nodes are involved. It is not uncommon to have as many as 30 lymph nodes removed during a colon cancer surgery. This is different from many other types of cancer, where far fewer nodes are removed.

Margins

Your report may comment on margins. This is the area at the edge of the specimen that was submitted. When performing a cancer surgery, the surgeon attempts to remove the entire tumor and some normal tissue surrounding it. This area of "normal tissue" is important because any stray cancer cells may be included in this. If the edge (or margin) contains tumor, there may have been cancer cells left behind. The goal of surgery is to achieve a "clear margin", that is, clear of any cancer cells.

Size

Your report may or may not specify the actual size of the tumor. While size can be important, in colon cancer, depth of invasion is most important.

Putting it all together

All of these pieces are used to determine the stage of the cancer and what treatment is needed. By understanding the basics of the report, you will be better able to discuss your treatment options with your healthcare team. The staging system most commonly used for colon cancers is the American Joint Committee on Cancer (AJCC) staging system. This system utilizes the
extent of the primary tumor (T0-4), the absence or presence of cancer in the lymph nodes (N0-2), and the existence of metastasis (M0 or 1) to assign a TNM rating, which corresponds to a stage. The TNM rating is broken down as follows:

**Primary Tumor (T):**
- **Tx:** Primary tumor cannot be assessed
- **T0:** No evidence of primary tumor
- **T1s:** Carcinoma in situ
- **T1:** Tumor invades submucosa
- **T2:** Tumor invades muscularis propria
- **T3:** Tumor invades through muscularis propria into pericolorectal tissues
- **T4**
  - **T4a:** Tumor penetrates to the surface of the visceral peritoneum
  - **T4b:** Tumor directly invades or is adherent to other organs or structures

**Lymph Nodes (N):**
- **Nx:** Lymph nodes cannot be assessed
- **N0:** No lymph nodes metastasis (spread)
- **N1:** Metastasis to 1 to 3 lymph nodes
  - **N1a:** Metastasis to 1 regional lymph node
  - **N1b:** Metastasis to 2-3 regional lymph nodes
  - **N1c:** Tumor deposits in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis
- **N2:** Metastasis in four or more regional lymph nodes
  - **N2a:** Metastasis to 4-6 regional lymph nodes
  - **N2b:** Metastasis to 7 or more regional lymph nodes

**Distant Metastasis**
- **M0:** No distant metastasis
- **M1:** Distant metastasis
  - **M1a:** Metastasis confined to one organ or site
  - **M1b:** Metastasis in more than one organ/site or the peritoneum

These ratings are combined to come up with a stage for the cancer. The Duke's staging system is an older system that is not as precise at describing the tumor, but you may still hear it used.

- **Stage 0** (also called carcinoma in situ) (TisN0M0): The cancer is confined to the inner lining (mucosa) of the colon or rectum.
- **Stage I** (T1 or 2, N0, M0): The cancer has spread to the muscular layer of the colon or rectum, but not to nearby tissue or lymph nodes. This is also called Dukes A colon cancer.
- **Stage IIA** (T3, N0, M0): Cancer has spread through the colon wall, but not to nearby tissue or lymph nodes.
- **Stage IIB** (T4a, N0, M0): Cancer has spread through the layers of muscle to the lining of the abdomen (peritoneum), but not to nearby lymph nodes.
- **Stage IIC** (T4b, N0, M0): Cancer has spread through the wall of the colon or rectum and has grown into nearby tissue, but not lymph nodes.
- **Dukes B colon cancer** is used to describe all stage II tumors.
- **Stage IIIA** (T1 or T2; N1 or N1c, M0) or (T1, N2a, M0): The cancer has spread through the submucosa or muscle layer and into 1-3 lymph nodes, but has not spread to other areas of the body.
- **Stage IIIB** (T3 or T4a, N1 or N1c, M0), (T2 or T3, N2a, M0), or (T1 or T2, N2b, M0): The tumor has grown through the colon wall or to surrounding organs/tissues and has invaded 1-3 lymph nodes, but has not spread to other areas of the
body.

- **Stage III C** (T4a, N2a, M0), (T4a, N2b, M0), or (T4b, N1 or N2, M0): Colon Cancer that has spread to 4 or more lymph nodes, but has not spread to other areas of the body.
- Dukes C colon cancer is used to describe all stage III tumors.
- **Stage IVA** (Any T, Any N, M1a): The cancer has spread to a single distant part of the body (i.e. liver, lungs).
- **Stage IVB** (Any T, Any N, M1b): The cancer has spread to more than one part of the body.

### Molecular Markers to Provide Further Guidance

A molecular marker is something found in the blood, tissue or other body fluid that is a sign of a normal or abnormal process, condition or disease. There are substances in some tumors that can gauge the likelihood of recurrence (prognostic marker) or predict a response to chemotherapy (predictive marker). Two molecular markers found in colon cancers have gotten some attention in recent years; "microsatellite instability" and "18q loss of heterozygosity" (LOH).

#### Microsatellite Instability

Microsatellite DNA consists of nucleotide sequences, repeated over and over and linked together, which are found in all human genes. Molecular testing can identify instability, or errors, in the microsatellite DNA of tumors, such as a change in the number of repeat sequences; this is called microsatellite instability (MSI). MSI is a way to measure a deficiency of mismatch repair (MMR) in tumor DNA. A deficiency of MMR results in an increase in mutations within the colon cells, which partly contributes to the development of colon cancer.

There are two reasons to test colorectal cancers for MSI. The first is to identify those at risk for hereditary non-polyposis colon cancer (HNPCC), a hereditary disorder that increases a carrier’s risk for other cancers, including endometrial, ovarian, stomach, pancreas, and kidney cancers and they should be screened accordingly. In addition, blood relatives of a person with HNPCC could also carry this genetic mutation and they may want to have genetic counseling and testing to determine how this affects their screening recommendations. The second reason for MSI testing is that knowing an early-stage colorectal cancer has MSI may change the way it is treated.

MSI testing identifies tumors as MSI-H (i.e. MSI-high), meaning they lack MMR proteins or are deficient in MMR proteins (dMMR), or MSI-stable and MSI-low, meaning they are considered MMR proficient (pMMR) or contain most or all of the MMR proteins. This information is especially helpful for those with stage II colon cancer. Studies have found MSI-H tumors are associated with a better prognosis. Approximately 22% of stage II colon tumors (but only 12% of stage III tumors) have MSI-H. Several studies have found that patients with stage II MSI-H tumors did not derive any benefit from 5-FU adjuvant therapy, and actually fared worse if they were treated with chemotherapy. This was true for stage III MSI-H tumors. MSI-stable disease, however, may benefit from 5-FU based treatment. Some experts recommend MSI testing as another tool to determine the need for treatment in stage II disease.

#### Other Markers

Humans have 23 pairs of chromosomes, for a total of 46 chromosomes, found in every cell in the body. Each chromosome contains over 1000 genes. Chromosome 18q contains two genes that are linked to tumor suppression. Over a person's lifetime, he or she can develop damage to genes or chromosomes due to exposures, such as smoking and viruses. Loss of one copy of chromosome 18q is called a loss of heterozygosity (LOH). Results of studies looking at the predictive value of 18qLOH have been conflicting. One trial found a greatly improved survival when no LOH was present (96% vs. 54%), but a subsequent trial did not confirm this, therefore further study is required. In addition, the current method of testing for 18q LOH is difficult to perform. More efficient techniques would be needed to make widespread use of this test feasible.

Other molecular markers being studied include KRAS, BRAF, a tumor suppressor called guanylyl cyclase 2, p53 and ERCC-1. Studies have found some of these markers to be useful in determining cancer treatment. For instance, anti-cancer medications that target the EGFR protein, such as, Cetuximab and Panitumumab, will not be effective in people who have a KRAS or BRAF gene mutation (defect). These tests are not the standard at this time, but some practitioners are using them, so you may hear them described to you.
Genomic Profiling

Genomic profiling, using a gene signature, is an analysis of the level of expression of a group of genes in the tumor tissue, which is then used to predict outcomes.

It is important to note that the genes being looked at are the mutated genes that are a part of the tumor, and not the entire set of genes that you inherited from your parents. Genetics is the study of genes that are inherited and passed on from generation to generation. These genes are responsible for many characteristics, including hair and eye color. Increased risk for certain diseases can also be passed on through genes. BRCA1 and BRCA2 ("breast cancer genes") are an example of this, and women with abnormal versions of these genes are at higher risk of developing breast cancer. The science used in the Oncotype Dx™ test is called genomics. This type of test looks at the genes that make up the tumor and evaluates how they interact and function. It looks at how active various genes are within the tumor, which may influence how the tumor grows and responds to treatment.

Genomic Health has developed a gene signature, called the Oncotype DX Colon Cancer Assay, with the goal of predicting risk of recurrence and benefit from 5-FU treatment for stage II colon cancer. In order to perform the test, scientists determine the levels of expression of 18 specific genes in the tumor tissue (13 of the genes are cancer-related: 7 to predict recurrence, 6 to predict 5-FU treatment benefit; the other 5 are used as "reference" genes). Based on the level of expression of each of these genes, two scores are assigned. The Recurrence Score™ and Treatment Score™ are on a scale of 0-100, with higher scores indicating a greater risk of recurrence or better response to therapy, respectively.

In order to determine if the gene signature is able to predict recurrence and treatment benefit in colon cancer, validation studies are performed. The validation study for the Oncotype DX test examined tumor samples collected in past studies where we already know the outcomes for the study participants. The company runs the gene signature test on these samples and looks at what outcome the Recurrence Score™ and Treatment Score™ would predict compared with the actual outcome.

The validation trial found that the Recurrence Score™ predicted the risk of recurrence in three groups, low (average 12%, range 9-16%), intermediate (18%, 13-24%) and high (22%, 16-29%) risk scores. The difference between the low and high groups was found to be statistically significant. In this study, the Recurrence Score™ and the Treatment Score™ did not accurately predict whether patients would obtain any benefit from treatment with 5-FU. Like many of the other "high-risk" features we have discussed, it is not clear if the Oncotype DX™ test can be used to make treatment decisions and further study is needed to determine the clinical usefulness of this test.

A second gene signature test is called ColoPrint, developed by Agendia and being studied for use in stage II and III colon cancers. Early reports have shown the ability to predict recurrence using this test. International trials are ongoing to determine if this test can be useful in treatment decision-making.

Other OncoLink Resources

Read OncoLink's Overview of Colon Cancer.

Read Stage II Colon Cancer: To Treat or Not To Treat?