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

A diagnosis of colon cancer brings about many emotions because of the uncertainty it causes; uncertainty about side effects, the ability care for ourselves, and most importantly, our life expectancy. A diagnosis of stage II colon cancer has an added concern - the question of whether chemotherapy following surgery is beneficial. You would think this would be an easy decision. In fact, studies have not found a clear answer to this question for many cases. Chemotherapy has side effects and we don't want to unnecessarily expose people to chemotherapy unless we are confident it is going to help them.

In stage I colon cancer, surgery to remove the tumor is the only treatment needed. Stage III tumors, which are tumors that have spread to the lymph nodes, are treated with surgery followed by chemotherapy (called adjuvant chemotherapy; it is given after surgery to reduce the risk of a recurrence of the cancer). This has been shown to lead to improved survival.

Stage II disease falls somewhere in between. An estimated 75% of people with stage II colon cancer will be cancer-free 5 years later, without adjuvant chemotherapy, but 25% will not. Some of these patients may benefit from having chemotherapy after surgery. So, how do we know which patients are most likely to benefit from chemotherapy? That is the million-dollar question, which we will take a stab at addressing here.

Staging Terminology

A tumor is staged using the "TNM" system, which incorporates the tumor size/depth, presence of cancer in lymph nodes and whether or not metastases are present. Stage II colon cancer includes tumors that are T3N0M0 or T4N0M0.

- T3 tumors invade through the muscularis propria (outer layer of the colon) and into the peri-colorectal tissues (tissue surrounding the colon).
- T4 tumors extend through the colon wall and attach to or invade a nearby structure or organs.
- N0 (N zero) means that no cancer cells were found in the lymph nodes.
- M0 (M zero) means that no metastases are present (no spread to other organs).
- When looking at lymph node status, you also want to know the number of lymph nodes that were examined by the pathologist (we'll discuss more on that later). For example, the report might state "fifteen benign lymph nodes (0/15)" or "tumor seen in sixteen of twenty lymph nodes (16/20)", meaning a total of 15 and 20 nodes were examined, respectively.

Note: In the past, the Dukes’ staging system was commonly used. Dukes B2 and B3 most closely correlate with Stage II in the TNM system. Currently, the Dukes system is no longer used in practice.

Not All Stage II Tumors Are Alike

Though stage II tumors are grouped together, there are some that appear more likely to come back after treatment and may benefit from adjuvant chemotherapy. There are some features of the tumor that increase the chance that the cancer will come back. If a tumor has these high-risk features, you should discuss with your provider the risks and benefits of adding chemotherapy after surgery. Studies have found only small improvements in survival (estimated to be between 2 and 5%) with the addition of chemotherapy in stage II disease. This has to be weighed with the possible side effects from the chemotherapy treatment. Therefore, each person must make his/her own educated decisions regarding treatment, based on the information available.

High Risk Features

A few “features” of a tumor have been found to put a person at higher risk of the cancer coming back. These features include:
- A T4 tumor – this size tumor has broken through the colon wall and into nearby tissues.
- If there is a bowel perforation or obstruction at the time of diagnosis.
- Grade 3 tumors – these appear very abnormal under the microscope. The grade is reported in the pathology report.
- Lymphovascular and perineural invasion – if the pathologist sees tumor cells in the tiny blood vessels lymph system and nerves around the tumor, it will be stated on the pathology report.
- Less than 12 lymph nodes were examined by pathologist.

The risk factors above are generally accepted as putting the patient at higher risk for recurrence and should prompt a discussion about adjuvant chemotherapy. There are some other factors that affect risk and play a role in whether or not to have chemotherapy. These include:

- Prior to surgical for colon cancer, a blood test for CEA (carcinoembryonic antigen) is done. CEA is a substance produced by the cancer cells, called a tumor marker. Elevated levels (CEA>5 ng/ml) prior to surgery are thought to infer a higher risk of recurrence. After surgery, CEA should return to a normal level. CEA is monitored in the months/years after treatment to look for recurrence, whether or not chemotherapy was received.
- Microsatellite Instability (MSI) status, which is classified as high (H) or low (L). Tumors with MSI-H status are thought to be less aggressive and may not benefit from the addition of chemotherapy.
- BRAF gene mutations may help predict more aggressive tumors. BRAF is described as wild-type or mutant. BRAF mutant along with MSI-L appear to be more aggressive than wild-type with MSI-H.
- Studies are looking at KRAS gene mutations and 18q loss of heterozygosity (LOH) to help guide therapy choices as well.

(You can learn more about all of the above features in the Understanding Pathology article)

**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. They are not the 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 genomic profiling 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.

A few companies have come up with a panel of tumor genes that can predict how likely the tumor is to recur after surgery. However, the tests have not been shown to be able to predict which tumors will benefit from chemotherapy. The tests can be expensive and may not be covered by insurance. Your provider can send information to your insurance company to request approval. These tests include:

- Oncotype DX Colon Cancer Assay – This test looks at 12 genes to predict the risk of recurrence. The sample is designated as low, intermediate or high risk.
- ColoPrint – This test looks at 18 genes and designates the tumor as either high or low risk for recurrence.
- GeneFx – This test looks at 482 genes and designates the tumor as low or high risk.

**Conclusion**

I did say it was the million-dollar question, didn't I? As you can see, there are a number of things to consider when treating stage II colon cancer. Studies continue to look at the benefits and risks of treatment and which treatments are superior. The best we can do is look at each patient and their tumor individually. You and your providers should consider the stage and features of the tumor, your medical history and your preferences about treatment. As an educated patient, you play a role in this decision-making process and need to make a decision you can feel comfortable with, using all of the information available.
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