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

A diagnosis of cancer brings about many emotions because of the uncertainty it causes: uncertainty about side effects, the ability care for ourself, and most importantly, our life expectancy. But with the diagnosis of stage II colon cancer even selecting the best treatment can be fraught with uncertainty. This is the case when it comes to the question of whether to get chemotherapy or not following the surgery-this is the "Million Dollar Question" in treating colon cancer. You would think this would be an easy decision, but in fact, studies have not found a clear answer to this question. And, as you can imagine, this is a critical question as chemotherapy has side effects and we don't want to unnecessarily expose people to chemotherapy unless we are confident the chemotherapy is going to help them. Let's examine the questions facing treatment decisions for stage II disease, and look at some of the ways in which physicians determine the answer for the person in front of them.

In stage I colon cancer, surgical resection alone is widely accepted as standard treatment, and no additional therapy is needed. Stage III tumors, which are defined as having cancer cells found in the lymph nodes near the tumor, are treated with surgery followed by chemotherapy (called adjuvant chemotherapy, meaning it is given after surgery to reduce the risk of a recurrence of the cancer), and this has been shown to provide a benefit in survival. Stage II disease, however, falls somewhere in between, and an estimated 75% of people with this diagnosis will be cancer-free 5 years later, without adjuvant chemotherapy. And while we lack data from clinical research studies to say that chemotherapy given after surgery for Stage II colon cancer improves survival, there may be individuals who could benefit from doing so. How do we know who is among the small percentage of patients most likely to derive a benefit from further treatment? 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 considered T3N0M0 or T4N0M0. T3 tumors invade through the muscularis propria (outer layer of the colon) into the pericolorectal tissues (tissue surrounding the colon). T4 tumors extend through the colon wall and adhere to or invade a nearby structure or organs. N0 ("N-zero) means that no cancer cells were found in the lymph nodes and M0 ("M-zero") means that no metastases are present (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 subgroups that appear more likely to relapse and may, in turn, derive more benefit from adjuvant chemotherapy. The 5-year survival for people with T3N0 tumors is 85% versus 72% for those with T4N0 tumors, yet these are both classified as stage II. A tumor may have other high-risk features that may predict a higher chance of recurrence. While the presence of these high risk features can prompt a discussion between the physician and patient about the use of chemotherapy, most clinical studies have found only small improvements, if any, in survival (2%-5%) with the addition of chemotherapy in stage II disease. Therefore, each person must make his/her own educated decisions regarding treatment based on the information available.

It is also important to note that stage II tumors have previously always been considered as just another phase of the same cancer and that stage II cancers just have disease extent that is between stages I and III. More recently, experts think it is possible that stage II tumors are genetically different than stage III tumors, which may explain the very different responses of
these tumors to the same treatments. While we have no definitive answers to this question, it is something to consider when looking at the various features of stage II and III tumors that predict recurrence and treatment benefit.

**High Risk Features**

As already noted, the depth of invasion (T3 vs. T4) is one high-risk feature. People found to have a bowel perforation or obstruction, at the time of diagnosis, are also at higher risk for recurrence. The "grade" of the tumor can also affect recurrence risk. When the tumor is examined by the pathologist, it is assigned a "grade", which tells how abnormal the cells appear. The more a tumor cell looks like a normal cell, the more well-differentiated it is. Grading is broken down into three groups:

- Grade 1: also called well differentiated. Cells appear the most similar to normal colon cells
- Grade 2: also called moderately differentiated.
- Grade 3: also called poorly differentiated. Cells appear the most abnormal and tend to grow more aggressively.

Grade 3, or poorly differentiated cells, are considered high risk. The pathologist may also identify invasion of the blood vessels, lymph nodes or nerves by cancer cells (lymphovascular or perineural invasion), which is considered high risk.

Prior to surgical removal, a blood test to detect 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.

Lastly, the number of lymph nodes examined can put a tumor in the high-risk category. If fewer than 12 lymph nodes are removed and examined, the risk of recurrence is higher and the overall survival lower. In studies, the 5-year overall survival (OS) correlates to the number of lymph nodes removed (1-7 LNs = 49.8% OS, 8-12 LNs = 56.2%, >12 LNs = 63.4%). It is not clear if this is because examining more lymph nodes in these patients would have found their tumors to be stage III, or because the surgical removal was less than complete, or perhaps both. We don't know for sure, but this finding often drives the decision to use adjuvant chemotherapy in patients with fewer than 12 LNs removed.

Studies have found that the presence of two or more high-risk factors is most likely to increase the risk of recurrence. In one study, patients whose stage II tumors did not have any high-risk features have been reported to have a 5-year survival rate of 95%. So as you can see, there are many things to consider when deciding whether or not to treat with adjuvant therapy.

Unfortunately, all of these "high-risk" features suggest an increased risk of recurrence and/or decreased survival. However, studies have not been able to show that the addition of chemotherapy provides any benefit, and professional guidelines are not in agreement. Two groups do not support the use of adjuvant chemotherapy for stage II disease, even in the presence of high-risk features, due to the very small benefit derived (2-5%) from this potentially toxic therapy. Meanwhile, a third professional group suggests that adjuvant chemotherapy should be considered for patients with high-risk features. Patients and physicians are often not comfortable choosing to forgo adjuvant therapy. Reviews have found that more than ¼ of patients with stage II disease receive adjuvant therapy, despite a lack of evidence that it improves survival.

**Is Chemotherapy Choice the Issue?**

Perhaps the problem is that we did not use the best chemotherapy regimens? The majority of trials in stage II disease have used fluorouracil (5-FU) based regimens – now that other chemotherapy agents are available, would they prove superior? The MOSAIC trial compared the standard 5-FU/leucovorin regimen to FOLFOX-4 (oxaliplatin, 5-FU/leucovorin) in colon cancer, with a percentage of these patients having stage II disease. The FOLFOX regimen did not decrease recurrence rates or improve overall survival at 6 years, compared to 5-FU and leucovorin alone. However, this trial did not have a control group of patients who did not receive chemotherapy, so we cannot determine if chemotherapy was better than observation. Another study by the NSABP (National Surgical Adjuvant Breast and Bowel Project) included patients with stage II disease in a study comparing weekly 5-FU/leucovorin with or without oxaliplatin every other week. There was no statistically significant benefit in survival for those with stage II disease.

**Molecular Markers to Provide 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. Are there substances we can identify in a tumor that can gauge the likelihood of recurrence (prognostic marker) or predict a response to chemotherapy (predictive marker)? Two molecular markers 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.

Tumors are identified 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. Studies have found MSI-H tumors are associated with a better prognosis and is present in approximately 22% of stage II colon tumors (but only 12% of stage III tumors). Several studies have found that patients with stage II MSI-H tumors not only did not derive any benefit from 5-FU adjuvant therapy, but they actually fared worse if they were treated. This was not seen for stage III MSI-H tumors. MS-stable disease, however, may benefit from 5-FU based treatment. Some experts recommend testing for MSI testing as another tool to determine the need for treatment in stage II disease.

**18q Loss of Heterozygosity**

Humans have 23 pairs of chromosomes, for a total of 46 chromosomes, in every cell. Each chromosome contains over 1000 genes. Chromosome 18q contains 2 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, so better techniques would be needed to make widespread use feasible.

Other molecular markers being studied include KRAS, a tumor suppressor called guanylyl cyclase 2, p53 and ERCC-1. Some studies have found these markers to be useful, however, further study is needed to determine their clinical usefulness.

**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 examines 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 ScoreTM and Treatment ScoreTM would predict compared with the actual outcome. In this case, the samples were taken from the Quasar trial.

The validation trial found that the Recurrence ScoreTM 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. Unfortunately, in this study, the Recurrence ScoreTM and the Treatment ScoreTM did not predict that 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.

**Conclusion**

I did say it was the million-dollar question, didn't I? As you can see, there is no easy answer. The best we can do is look at each patient as an individual; consider the stage and features of the tumor, the patient's medical history and 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.