Risk Assessment in Stage II Colorectal Cancer

In the treatment of colon cancer today, the decision-making involved in the treatment of stage II disease is probably the most challenging aspect. The major question is whether or not these patients should receive postoperative adjuvant chemotherapy. Approximately 75% of stage II colon cancer is cured by surgery alone. For the remaining 25% of cases, there is great debate over whether adjuvant chemotherapy is sufficiently effective in enough patients to warrant the exposure to potentially toxic treatments. In the important QUASAR clinical trial, stage II patients were randomized to either fluorouracil (5-FU)-based therapy or observation. The results demonstrated an approximate 3% improvement in outcome for the 5-FU-treated patients. This leads to the assumption that treating all stage II patients with adjuvant chemotherapy is gross overtreatment, when essentially 97% of these patients will not benefit. Clearly the only way to approach this decision is through risk determination. In this article, I will describe the current state of defining high- and low-risk disease, which is mainly through histopathologic characteristics, as well as discuss emerging approaches such as molecular markers and genomic profiling.

Possibly the most difficult and confusing subject in colon cancer today is the decision-making involved in the treatment of stage II colon cancer. The pendulum has been swinging back and forth over the past several decades as to whether stage II colon cancer patients should receive postoperative adjuvant chemotherapy or not.

Which Stage II Patients Should Receive Treatment?

The issues themselves are simple. Surgeons cure stage II colon cancer approximately 75% of the time, which of course is a fairly good number. However, this leaves 25% of the patients who will ultimately die of their disease. Postoperative adjuvant chemotherapy has been given to these patients and, in a series of clinical trials, has demonstrated a small but measurable improvement in outcome. The most important of these, and the only one that was adequately powered to answer this question, is the QUASAR (QUick And Simple And Reliable) clinical trial.[1] In this trial, mostly stage II colon cancer patients were randomized to either fluorouracil (5-FU)-based therapy or observation. The results demonstrated an approximate 3% improvement in outcome when 5-FU was administered to this patient subset. Said another way, 97% of patients were exposed to chemotherapy without any benefit. So, it also raises the issue of whether or not all patients with stage II colon cancer should be exposed to chemotherapy, knowing that only 3% of them will benefit from the treatment (Figure 1). This is clearly an overtreatment of most of the patients given that 97% of them will not benefit from the therapy administered. However, given that the 3% are, in essence, cured of their disease, these are high-stakes gambles that most patients will accept.
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Adjuvant therapy for colon cancer *fails* 97% of the time in stage II colon cancer. Gold arrow: We are undertreating patients; red arrow: We are overtreating patients. QUASAR *Lancet* 355(9215):1588-1596, 2000. Used with permission.

In the world of breast cancer, there are several studies that point to even as low as 1% benefit rate that patients will accept as justification for receiving adjuvant chemotherapy.[2] Similar studies have been performed in colon cancer but are not yet published. The world of decision-making in stage II colon cancer, in my opinion, is a lot like religion. You either believe that it is appropriate to treat these patients, treating them similarly to stage III patients and recognizing the benefit rate is less, or you believe that this is an inappropriate use of our resources and exposure of patients to toxicity and, therefore, unwarranted. You either believe or you do not.

Further confusing the arguments, we have long felt that stage II colon cancer was simply a step on the path from stage I on to stage III disease, that each of these stages represents a continuum of, in essence, the same cancer with new additional genetic abilities of metastasis being acquired.[3] Newer evidence, however, contends that it is possible that stage II colon cancer is genetically different than stage III colon cancer, that they are in fact different cancers genetically.[4] This raises a further complicating factor as to whether these patients should even be included into routine adjuvant clinical trials. Maybe that is why the results are different between the stages. There is a great deal of debate on an international level between cooperative groups as to whether stage II colon cancer should be included, with the NSABP (National Surgical Adjuvant Breast and Bowel Project) and European groups often including stage II colon cancer, whereas others, such as the Southwest Oncology Group (SWOG) and Cancer and Leukemia Group B (CALGB), not including stage II patients in their adjuvant trials. It is unclear who is right in this argument.

Let us begin by looking at our current ways of stratifying patients. Clearly what we need is a way to determine which patients are in the high-risk category and therefore should be given chemotherapy, and those who will not have recurrent disease and are therefore in the low-risk category. There has been a great deal of focus on this over the past several years, and as a result, I think we are left with more questions than answers.

**Defining High-Risk Stage II Colon Cancer**

Our current determination of high-risk and low-risk stage II colon cancer is purely based on histopathologic characteristics. Based on data that have come forward over the past 2 decades, we looked at patients with T4 lesions, those who have had obstruction or perforation, those with lymphovascular invasion, and those with poorly differentiated histology as being high-risk patients. These are all quite gross measures (if one considers our expanding understanding of the molecular biology of cancer) to determine who is in trouble and who is not. For example, one obvious flaw in this strategy of risk assessment is microsatellite unstable tumors. These tumors typically have poorly differentiated histologies that would put them in the high-risk category by that measure, but we know that MSI-H (microsatellite instability–high) tumors have a better prognosis and may actually not benefit from chemotherapy at all.[5] Here our molecular biology insights are in stark conflict with...
our current risk assessments. So these gross measures of delineation of high and low risk based on purely histopathologic testing are not going to serve us well in the long term.

**Lymph Node Count**

A more recent focus has taken us to the lymph node count in a patient’s specimen, with a cutoff now being somewhat arbitrarily set at 12 lymph nodes.[6] Data suggest that the more lymph nodes that are collected, the better a patient’s prognosis.[7] This is most pronounced in stage II disease. It is unclear why some patients have more lymph nodes than others, with the debate being that it is possibly the surgeon’s fault, possibly the pathologist’s fault, or even possibly the patient’s fault. However, the data do suggest that those with higher numbers of negative lymph nodes have better prognosis. Is this nothing more than an appropriate assignment of the stage of the patient? It is certainly possible that as more lymph nodes are sampled, the likelihood of truly being a stage II vs a stage III increases.

Newer assays have been developed to try and look at this even further. Studies have been done looking at microscopic tumor deposits within lymph nodes; these studies have demonstrated that patients with microscopic disease do behave more like stage III patients.[8] Therefore, these data suggest that we should analyze our tumors to this level if at all possible. This new assay is available but has not been widely incorporated into practice at present, but it is certainly something we need to continue to consider in making decisions for our patients.

**Molecular Markers: (MMR)**

Most recently, based on small retrospective analyses, genetic and molecular markers have emerged that might be useful and, of course, we believe are the future for detecting who is at risk and who is not at risk. The leading molecular marker for determination of risk is microsatellite instability. Colon cancer has been thought of as one disease that comes from polyps through the familial adenomatous polyposis (FAP) mutation mechanism. However, more recently stemming from evidence from hereditary non-polyposis colorectal cancer (HNPCC or Lynch syndrome), it is recognized that as many as 20% of patients develop colon cancer through this completely different genetic pathway.

In the HNPCC patient, we know that they have genetic abnormalities that lead to microsatellite instability. These patients represent 5% to 6% of all patients with colon cancer and therefore are a large patient base; we will all see several patients with this inherited syndrome. In addition, as many as 15% of all sporadic stage II colon cancer patients have loss of function of these genes, namely, MLH1, MSH2, MSH6, or PMS2, leading to microsatellite instability—not a germ-line mutation but an acquired defect in the tumor.[9] FIGURE 2

![FIGURE 2](image)

Overall survival stage II (55%) or stage III (45%) colon cancer according to treatment status (570 pts) Ribic C et al: *N Engl J Med* 349:247-257, 2003. Used with permission.

Important retrospective analyses looked at the role of MSI in patients with colon cancer, particularly stage II colon cancer. These studies by Ribic[10] and Sargent[9] both demonstrated that patients who had microsatellite-unstable tumors had a much better prognosis and were not responsive to 5-FU chemotherapy. In fact, both of these studies also demonstrated that 5-FU–based chemotherapy resulted in a poorer outcome for those patients than those who were left untreated (*Figures 2* and *3*). This suggested that, somehow, chemotherapy in this genetic group (representing 20% of all colorectal cancer) was harmful and therefore should be avoided. Interestingly both authors
suggested that this was specific for stage II disease and did not find the same for stage III, although a large cautionary note must be raised as the numbers in all of these samples were quite small. As a result, prospective studies are now being performed using MSI genetic determination as an assignment factor for treatment: patients with MSI-positive stage II colon cancers are being assigned to observation, whereas those with microsatellite-stable (MSS) tumors would be given chemotherapy with a combination regimen of 5-FU and oxaliplatin (ECOG 5202). The assignment of patients to treatment based on their genetic profile is exactly how we should proceed, using these markers as prospective tools. Although we may fight about the actual design of this clinical trial, we must also support it fully as it is the only way we will learn which patient should be treated or not.

More recent data from the PETACC-3 (Pan-European Trials in Adjuvant Colon Cancer) trial suggest that chemotherapy given to MSI patients was not harmful but did not benefit these patients.[11] I think the jury is still out on the harm chemotherapy does in MSI patients in stage II disease. The data are fairly strong that MSI is a predictor for lack of benefit of 5-FU in patients with stage II colon cancer. Its role in stage III disease is much more controversial and not actively being studied in a prospective manner.

Molecular Markers: Genomic

Most recently, genomic profiling has become the hot area for research in determining who should receive chemotherapy and who should not. We are all appropriately optimistic about the Oncotype DX assay that was used in breast cancer. In this setting, using a series of a small number of genes, breast cancer patients were profiled both for prognostic and predictive factors.[12] In specific, the genomic profile can determine who is at high risk as well as who is going to benefit from chemotherapy.[13] This is clearly useful positive information that could be incorporated in real time in patient decision-making and is quickly being incorporated into routine practice in the breast cancer world today.

A similar analysis was performed using the QUASAR data that I referred to earlier. In this case, a series of patients were profiled comparing those who received surgery only and those who received surgery plus 5-FU and leucovorin. Starting with a panel of 761 genes four large development studies (NSABP C01/C02, C04, C06, and Cleveland Clinic) were conducted to identify genes related to recurrence and treatment benefit with 5FU/LV. Through a selection process that narrowed down the gene list to 18 genes, it was hoped that we would have a genomic profile that would be both prognostic for recurrence (Recurrence Score) and predictive (Treatment Score).[14] Unfortunately the treatment score did not prove to be predictive in this clinical trial, so it was not able to distinguish those who were benefitting from chemotherapy and those who were not. The prognostic genes did result in a positive outcome, particularly for those patients who had T3 lesions or who were mismatch repair (MMR)-proficient or microsatellite stable. These results were presented at the 2009 annual meeting of the American Society of Clinical Oncology. They suggested that we may have a new tool for stage II patients to help determine risk and therefore help decide whether to give chemotherapy or not. Patients with stage II disease that had T4 lesions had much higher risks, and therefore the feeling was they should receive chemotherapy. But those who were microsatellite-unstable or MMR-deficient had such a good prognosis that it was unlikely we would give them chemotherapy and therefore not worth measuring in that patient group. But the patients with MSS tumors, adequate nodal counts, and no other high-risk features—a group I call “vanilla stage II colon cancer”—were separable, from a low risk of 10% to a high risk of 25% relapse rate. It is likely that this 12-gene Oncotype DX colon cancer assay will be available for use in the coming year, so it is important to understand its value in decision-making in stage II disease.

In a very similar way but using different methodology, the group from Agendia has developed a ColoPrint similar to the MammaPrint assay that was developed for breast cancer.[15] This assay requires fresh tissue, making it a little bit more difficult to perform compared to the Oncotype DX.
assay which could be done on fixed tissue, but nonetheless, emerging data from this assay showed the ability to separate stage II patients according to their genetic profile. Ongoing international clinical trials incorporating ColoPrint into treatment decision-making are being performed, and may add further to our ability to see into a patient’s future—understanding who should receive chemotherapy and who should not in stage II disease.

Conclusions

Adjuvant therapy in colon cancer is very confusing at present. We have prognostic factors such as MSI, nodal counts, differentiation, and soon genomic profiling. What is the trump card in the game? It will be important to understand which factors are important and how to use them together. For example, if you had a patient with a T2N0 (0 of 7 nodes)—a stage I patient—would the low number of nodes trump everything and therefore we should give chemotherapy? What about an MMR-D tumor with perforation? Do we hold due to the MSI status or treat on the grounds of the perforation? I honestly do not know. But we will know eventually as we have started asking the correct questions. We are now finally focusing on the key genomic profiles that are going to be necessary to make decisions. Clearly patients need to have better information about their own personal risks. Once we have this, we will minimize the number of patients who are receiving chemotherapy needlessly, and we can focus down on the patients who are at the highest risks, ultimately knowing those who will relapse and those who will not. This will speed our clinical research, shorten the time for new drug discovery, and improve our cure rates for patients with stage II colorectal cancer.

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References:

REFERENCES


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