Approximately 150,000 new cases of colorectal cancer were expected for the year 2009 in the United States. Moreover, 49,920 deaths related to colorectal cancer were also predicted for the same year. The age-adjusted cancer death rates related to colorectal cancer have steadily declined over the past 2 decades. This improvement is a direct consequence of advances in prevention and treatment, including colorectal cancer screening, diagnostic tests, surgical technique, adjuvant therapies, and medical support.

The prognosis of colorectal cancer varies in accordance with disease stage and tumor site. While the 5-year overall survival for patients with stage I colon cancer can reach values close to 100%, it can be as low as 15% for stage IV patients.[3] Patients with stage II colon cancer are cured with surgery alone in 75% to 80% of cases. This means that if all patients with stage II tumors are referred to a medical oncologist, a large number will receive treatment that is not necessary. If none are referred, some will be undertreated. The benefit is small and treated patients are exposed to significant potential toxicity. The question is how to identify those who will benefit.

The present guidelines issued by the National Comprehensive Cancer Network (NCCN) for stage II colon cancer include the following[4]:

- Observation
- 5-FU/leucovorin or capecitabine (Xeloda)
- 5-FU/leucovorin/oxaliplatin (for high-risk features)
- Clinical trial

It is estimated that 30% to 35% of patients with stage II colon cancer receive adjuvant therapy. At present the decision to give chemotherapy is subjective, based on a limited set of clinical and pathologic markers, which are uninformative for the majority of patients. Other factors considered are the patient’s age, comorbidities, and the patient’s individual preferences.

The present markers of risk of recurrence are elements of the pathologic evaluation of the tumor, ie, tumor stage, tumor type, grade, margins, lymphovascular invasion, and perineural invasion. These measures carry different weight in individual patients and constitute the prediction of outcome. There is lack of consensus and standardization of individual elements that inevitably compromises the quality of the pathologic data. Treatment is advised for those patients thought to be at higher risk on the presumption that they will have a greater absolute benefit.

**Surgical Pathology**

**T Stage**

Despite being the best and the most widely used prognostic indicator, the TNM staging system has an accuracy of approximately 65% and therefore fails to estimate the risk of disease progression for many patients. The failure occurs primarily in stage II, where 5-year overall survival ranges from 30% to 80%.[5,6] As a result there is no consensus with respect to the indication of adjuvant treatment for those patients. In the 6th edition of the American Joint Committee on Cancer’s AJCC Cancer Staging Manual (AJCC-CSM), stage II was subdivided into IIA and IIB on the basis of whether the primary tumor was T3N0 or T4N0.[7]

Due to the prognostic variability of IIB patients, the 7th edition of the AJCC-CSM subclassifies T4
lesions into T4a (tumor penetrates the surface of the visceral peritoneum) and T4b (tumor directly invades or is histologically adherent to other organs or structures). Therefore, stage II patients are now classified as IIA (T3N0), IIB (T4aN0), and IIC (T4bN0).[8]

Although this reclassification should help in differentiating prognosis among stage II patients, there are other factors that can help in identifying patients likely to have a worse prognosis.

**T4 Lesions**

Colon cancer invading other structures accounts for approximately 10% to 20% of all colon cancers. These tumors often have aggressive tumor biology and their treatment carries a higher operative morbidity and mortality. Many of these are stage II lesions. Adequate surgery for this group of patients is an en bloc resection, and consists of removal of the primary tumor with all involved structures in a single specimen with clear surgical margins.

**TABLE 1**

<table>
<thead>
<tr>
<th>Predominant Tumor Grading System</th>
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<tbody>
<tr>
<td>Gland Formation</td>
</tr>
<tr>
<td>Well-differentiated</td>
</tr>
<tr>
<td>Moderately differentiated</td>
</tr>
<tr>
<td>Poorly differentiated</td>
</tr>
<tr>
<td>Undifferentiated</td>
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</tbody>
</table>

**Lymph Nodes**

Nodal stage is the most important indicator of the need for adjuvant chemotherapy. If a patient is node negative after only a few nodes have been examined, the likelihood of understaging is high. This concern has led to the recommendation that a minimum of 12 nodes be analyzed in every cancer specimen before assigning stage II.[11-14] The accuracy and predictive value of nodal staging is subject to the diligence of the surgeon on the extent of resection, as well as the pathologist in harvesting all the lymph nodes. One hundred years ago, Doctors Jamieson and Dobson stated, “No operation for malignant disease can be considered complete without the removal of lymphatic glands.” There is little controversy that this statement is the basis for the oncologic principles of an adequate colectomy for colon cancer.[15]

A standard colectomy for colon cancer consists of ligation of the primary artery at its origin with a complete lymphadenectomy of the segment in which the tumor is located. These principles must be followed regardless of the cancer stage and are able to provide sufficient lymph nodes for an adequate pathologic examination.[8,15,16]

Several efforts have been made to improve the surgical technique and consequently the prognosis. In 1954, Cole et al,[17] among others, reported finding cancer cells in the portal venous blood of a colon cancer patient. This observation gave rise to their suggestion that the vascular pedicle should be ligated before significant operative manipulation is undertaken.

In 1967, Turnbull et al[18] described the “no-touch isolation” technique. It consisted of high ligation of all lymphovascular pedicles prior to any tumor manipulation. The rationale behind the procedure was that tumor manipulation during the operation could potentially disseminate cancer cells through the mesenteric vessels and finally portal circulation. As a result, performing the ligation of all lymphovascular pedicles as a first step would be likely to decrease the rate of distant recurrence. Although there is a rational theoretic basis for its use, some authors failed to confirm the impact of the “no-touch isolation” technique on cancer outcomes.[19] These and other techniques have been described, but not proven unequivocally to be of prognostic value.

**Lymphovascular Invasion**

Venous invasion has been shown to be stage-independent as an adverse prognostic factor.[20]
Extramural vein invasion has been shown to be an independent indicator of unfavorable outcome and an increased risk of hepatic metastasis.[21] The significance of intramural venous involvement is less clear.

Lymphatic invasion[22] and perineural invasion[23] have been shown by multivariate analysis to be independent indicators of poor prognosis. However, it is not always possible to distinguish lymphatic vessels from venules. The expertise of the pathologist is important in recognizing malignant cells and differentiating histologic artifacts caused by the processing but lack of standardization and interobserver variation in these situations remains a major issue. Perineural invasion is almost always associated with a high tumor grade but there is no consensus on its value as a prognostic indicator.

**Tumor Grade**

High tumor grade (poor differentiation) has been shown in some studies to be associated with worse outcome; however, it is known that tumor grade can be confounded by relationships with other prognostic markers, including mismatch repair deficient tumors, which have excellent prognosis but are characteristically high grade. Reporting of tumor grade is complicated by the presence of different schemes without any consensus; in general tumor grading is based on the degree of gland formation and architectural and cytologic factors. In practice, there are different schemes without any consensus.

The length of resection margins required for an adequate colon cancer removal depends on the extent of intramural tumor spread beyond its macroscopic edge. It is still unclear how far intramural tumor spread occurs. Also, there is no agreement on the ideal way to measure the surgical margin (ie, in vivo, fresh tissue, fixed specimen).[24]

**Conclusion**

With the current state of knowledge our ability to evaluate risk and identify patients with stage II colon cancer who should be referred to a medical oncologist is subjective and qualitative. It includes assessment of the qualitative aspects of the pathology reports, the patient’s suitability to receive potentially toxic medication, and their personal preference. There is a need for quantitative and individualized information to help in predicting prognosis.

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