Colon cancer remains one of the most common human malignancies, with an annual global incidence of slightly less than 1 million patients per year.

As well-outlined by Drs. Beavan and Goldberg, in the past 20 years, the outlook for these patients has gone from pessimism that anything more than surgery was useful to certainty that we can markedly decrease the risk of recurrence. At least some steps have been made in clearly identifying which patients should receive adjuvant therapy. There is general agreement on current effective regimens, alternatives have been developed for patients who are unable to tolerate optimal regimens, and there is promise that future regimens may be more effective.

On the other hand, we are still unable to predict which patients have been cured by operation alone and which require additional therapy; we are unable to choose the optimal regimen for the individual patient; and we do not have adequate predictive markers for minimizing toxicity. In all, we have come a long way but still have a considerable distance to travel.

Looking Back
Drs. Beavan and Goldberg succinctly summarize the state of the art in the mid-1980s. Fluorouracil (5-FU) had already been studied for several decades. It offered modest palliation for patients with advanced disease but had no clear benefit when given as adjuvant therapy. There was considerable debate as to who should be treated and who should not be treated, with some studies still allowing the enrollment of patients with stage I disease. It was known that there were differences in toxicity depending on how 5-FU was given, with some ink-ling as to what might be causing those differences, but the optimal duration of treatment, method of administration, and technique of administration were still controversial.

By the early 1990s, the first clear evidence that postoperative adjuvant systemic therapy improved outcome was available. As Drs. Beavan and Goldberg point out, a moderately sized (by current standards) but carefully done controlled study demonstrated that 5-FU plus levamisole (an agent no longer important in colon cancer therapy) clearly decreased the risk of recurrence and reduced the risk of death. This single trial probably played the most important role, at a national consensus conference, in changing the standard of care for stage III colon cancer.

The remainder of the 1990s was spent refining 5-FU-based adjuvant treatment. For patients with stage III disease, 5-FU plus leucovorin given for 6 months became the standard of care. The best method of administering this agent remained controversial, with infusional vs bolus 5-FU studied by a number of investigators.

Current Practice
In the end, a combination of the two routes has become fairly widely used. Despite considerable effort, the use of systemic adjuvant therapy for patients at moderate risk (the majority of stage II patients) was and remains controversial. It is of interest that, as Drs. Beavan and Goldberg point out, several combined analyses have indicated that the additional increase in cure rate for patients with stage II colon cancer using 5-FU/leucovorin-type regimens vs surgery alone is approximately 3% to 5%. Whether or not this is clinically significant has been debated by gastrointestinal oncologists. On the other hand, for women 50 to 69 years of age with early-stage breast cancer, an improvement in outcome with adjuvant cytotoxic chemotherapy is of roughly the same degree (3%-5%) at 15 years.[1] In breast cancer, there is less controversy regarding the use of cytotoxic adjuvant regimens that are at least as toxic as 5-FU and leucovorin.

Drs. Beavan and Goldberg also point out that our previously accepted paradigm regarding the use of
postoperative adjuvant therapy on the basis of efficacy in more advanced disease may need to be reconsidered. For most solid tumors, the development of adjuvant therapy is based on treatments that are effective in palliating metastatic disease: Effective palliative therapy is expected to prevent recurrence in earlier stages of the same cancer, resulting in improved cure rates.

In colon cancer, one would assume that if two treatments—A and B—are equally effective in palliating stage IV disease, and treatment A is effective as adjuvant therapy, treatment B must also be effective. In fact, carefully performed prospective clinical trials have demonstrated that, at least from the information currently available, this is not true for colon cancer. While oxaliplatin (Eloxatin) when delivered in the FOLFOX regimen (leucovorin, 5-FU, oxaliplatin) or as used in the National Surgical Adjuvant Breast and Bowl Project (NSABP) trial clearly improves outcome, particularly for patients with stage III disease, irinotecan (Camptosar) in two large prospective trials and one smaller study did not. Before adopting a new treatment as a standard care option, carefully performed adequately powered clinical trials are essential.

Sargent and colleagues recently addressed an important issue in clinical trials drug development and in the drug approval process—whether a validated surrogate for improved outcome other than 5-year overall survival could be identified.[2] In a large meta-analysis, they clearly showed that patients who were free of disease at 3 years were highly likely to be alive at 5 years. Thus, 3-year disease-free survival is a reliable end point for assessing the effectiveness of adjuvant therapy in colon cancer, accurately predicting 5-year overall survival. This has important implications for the speed at which we can make decisions regarding the efficacy of new therapies.

Predictive Markers
Finally, as pointed out by Drs. Beavan and Goldberg, predictive markers for efficacy as well as toxicity represent an important area for future investigation. In other solid tumors such as breast cancer, predictive markers have long been accepted as means of guiding therapeutic options. This includes the measurement of HER2 to decide whether trastuzumab (Herceptin) should be used and the long-standing strategy of estrogen- and progesterone-receptor protein analysis to determine whether hormonal therapy would be useful. Preliminary data from common tumors such as lung cancer suggest that the administration of epidermal growth factor receptor kinase inhibitors may one day be based on the presence or absence of a mutation in the molecular target.[3]

Early findings in less common tumors such as gastrointestinal stromal tumor and glioblastoma multiforme indicate that analysis of a limited set of molecular markers or genetic abnormalities may predict outcome.[4,5] Such data have not yet been established in colon cancer. Immuno-histochemistry is not an accurate predictor for the use of cetuximab (Erbitux); a recent study failed to demonstrate that microvessel density, vascular endothelial growth factor levels, or thrombospondin—2 levels correlated with outcome for patients who received bevacizumab (Avastin) as a portion of their treatment.[6]

Technical correlative analyses conducted in colon cancer studies are acknowledged (eg, in the bevacizumab correlative marker study, the bulk of the tissue examined was from the primary tumor, not from metastatic sites). However, we do not yet have reliable predictive markers in colorectal cancer. Nonetheless, proof of principle from breast cancer and preliminary data from other tumors as outlined above gives us hope that similar predictive markers will be developed for bowel tumors. Functional imaging (for example, with positron-emission tomography-computed tomography) is undergoing intense study as a technique for obtaining a more rapid answer as to whether a given therapy, once initiated, is effective in an individual patient. As we have an increasing number of agents that are effective against colon cancer, rapid decision-making may be possible prior to therapy or at least soon after it has begun.

Finally, in addition to predicting outcome, physicians would like to avoid using therapy that is likely to be toxic. At least two possible predictive markers for excess toxicity have been identified in patients receiving therapy for advanced or localized colon cancer: low levels of dihydropyrimidine dehydrogenase (DPD) are associated with increased risk of 5-FU toxicity; polymorphisms of uridine diphosphate glucuronosyl transferase—1 (UGT1A1) have been associated with increased toxicity to irinotecan.

Conclusions
All in all, Drs. Beavan and Goldberg have nicely summarized increasing progress in treating one of the most common malignancies. The pace of improvement will hopefully continue at least at this rate, so that in 20 years we should be far ahead of where we are today.
Disclosures:
The author(s) have no significant financial interest or other relationship with the manufacturers of any products or providers of any service mentioned in this article.

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