

# ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

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## Colorectal Cancer In Focus

### Improving the Staging System in Colorectal Cancer

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**H&O** Describe the current staging system and what has happened to require a change in the system?

**GP** The system that is universally used to stage colorectal cancer (CRC) is based on a TNM (tumor, lymph node, metastasis) classification. The current version that is in use is the 6th edition of the American Joint Committee on Cancer (AJCC) guidelines, published in 2002. A recently published 7th edition will take effect on January 1, 2010. The problem with the 6th edition is that it suggests that if CRC spreads beyond the regional lymph nodes of the colon, the prognosis is worse than if it had not metastasized distantly, which we no longer believe to be true. In the current edition, if the cancer has not metastasized and is just through the wall of the colon, it is referred to as stage 2; if the cancer involves the lymph nodes, it is stage 3. Within stage 3, the tumor is stratified by the level of lymph node involvement: from a few nodes next to the primary location to nodes right up to the resection margin.

The limitation that we presently face is that everything beyond this point is stage 4; there is no stratification within this stage, and thus it includes a whole range of patients with different levels of disease. For example, a patient who has a potentially curative resection of their primary CRC, but then develops a small metachronous solitary metastasis in the liver, has a life expectancy of 2–3 years if left untreated. If the metastasis is completely excised, the patient has a greater than 50% chance of being cured; yet this patient is classified as stage 4. Furthermore, a patient who presents with CRC with multiple liver and lung metastases and peritoneal disease is also

classified as stage 4. This patient has incurable disease and, if left untreated, has a life expectancy of 6–9 months. However, with chemotherapy, the expectancy is closer to 18 months. Both of these patients, although they have different levels of disease and prognosis, are classified as the same stage. This type of classification was acceptable 20–30 years ago when there were much fewer treatment options, and patients who developed metastatic CRC beyond the lymph nodes had grim prognoses.

The situation has, however, drastically changed. We now have very effective drugs that as single/doublet regimens are giving patients a median of 2.5–3 year survival. In the past 10 years, we have seen the development of irinotecan and oxaliplatin, and more recently bevacizumab (Avastin, Genentech), cetuximab (Erbix, Imclone), and panitumumab (Vectibix, Amgen). More importantly, we have completely changed the outlook for patients with metastatic disease by moving patients whose liver disease appears unresectable at diagnosis into potentially becoming surgically resectable. At present, 20% of patients with liver metastases are resectable right away, and 30–40% could be made resectable with modern medical oncology.

It is now well known that patients who have surgery do quite well; resection of liver metastases results in a 5-year survival rate near 50% and a 10-year survival rate well above 25% and rising. Similarly, if lung metastases are resected, data show that 5-year survival is approximately 40%, and the 10-year survival mirrors liver metastases resection. Historically, only a very small percentage of patients with liver and lung metastases would undergo surgery. Presently, we resect as much liver as possible, ensuring that 25–30% of the liver volume is left behind and appears to be disease free. Because of advancements in surgical techniques and drug development, metastatic CRC patients are living longer, and there is an apparent need for an updated approach to staging these patients appropriately.

## H&O What are some of the current proposals for a new staging system?

**GP** Over the last few years, we have published a series of controversial reviews discussing current management of metastatic CRC patients and possible ways to amend the outdated staging system. One of the issues brought up in our reviews was: how to handle patients who are stage 4 and unresectable but become resectable when treated with chemotherapy. In the current system, these patients remain stage 4—they are not downstaged to resectability. We do not have a definition for this phenomenon, but we refer to the strategy as induction chemotherapy. Basically, we are taking patients who have an incurable prognosis and transferring them into a potentially curable prognosis; thus there is a need to differentiate between patients with potentially curable and incurable disease.

A few years ago, we published a review in *Journal of Clinical Oncology* proposing a reclassification within stage 4 to 4R (resectable) and 4U (unresectable). In the second review published last year, we proposed a modified TNM grid-based system. In this staging system, we suggested stratifying patients as resectable, initially unresectable, and unlikely to become resectable. This system was based on a consensus of experts rather than real evidence and is somewhat complicated, and thus has not been taken up widely.

Recently, we have reported results of a large population-based, non-single center–biased study done in England, in which we evaluated a cohort of 70,000 patients diagnosed with CRC between 1998 and 2002. We collected outcome data on all patients and followed the study population through 5-year survival. We found that in this group of patients, those that presented 10 years ago (at which time we did not use modern adjuvant chemotherapy regimens and were not performing total mesorectal excision surgery) with stage 3 CRC had a 5-year survival rate of approximately 45%. Now, the 5-year survival is considerably higher. We also looked at patients who presented with stage 4 CRC at that time, and their 5-year survival was approximately 5–6%. We then analyzed 1,700 patients who presented with stage 4 disease or subsequently became stage 4 and looked at their 5-year survival after liver resection: it was found to be over 50%. Based on these results, we determined that patients with surgically resectable metastatic disease, regardless of site, lymph nodes, or metastasis (liver and probably lung), should be classified as stage 3, because stage should reflect prognosis. Thus, my present view, based on the population data, is that we should label patients stage 3 for resectable metastatic disease

regardless of anatomic site of metastases and number of operations that may be necessary to eradicate the disease. Stage 4 should be kept for patients who have surgically unresectable metastatic disease. However, if these stage 4 patients are given chemotherapy to which they respond well and become surgically resectable, they would be downstaged to stage 3.

## H&O What kind of role will prognostic factors play in future staging systems?

**GP** The classic prognostic markers that have been around for years, including liver metastases (size, number, distribution) and histologic analyses (well, moderately, and poorly differentiated), have not changed and are inferred in the current TNM staging. Where we hope to go next is molecular markers, such as KRAS and BRAF. For example, we know that cetuximab will not work in a patient whose tumor is KRAS wild-type or in a patient who has a BRAF mutation. Therefore these are predictive markers. Incorporating these molecular markers in future staging systems will be necessary as we discover more mutations that prognosticate treatment choice and predict outcome. In the next 10 years, I think we will be constructing a 3-dimensional model of morphologic markers against molecular markers to more accurately predict prognosis. I suspect that eventually we will be able to look at a patient's genetic sequence and combination of mutations and determine their treatment options.

## H&O What possible benefits will a new classification confer?

**GP** The most important benefit is awareness. What we learned from the population-based study that we conducted is that of all CRC patients in England, approximately 6% undergo a liver resection. However, historically there has been a 7-fold difference in referral rates for liver resection between the lowest and highest referring hospitals. In the centralized system of England, only 18 designated hospitals across the country perform and are reimbursed for liver surgery. In the United States, it is more difficult to organize this kind of system, due to a different reimbursement structure and the geography of the country. England is geographically small with a very high population density, so it is easier to set up this type of program; in the United States, there are many remote areas where the level of awareness may be lower than in populated cities. Once we are able to educate people and bring more attention to the benefits of surgery, we will be able to perform more potentially curative resections and thereby increase survival time.

**H&O** What are the challenges to implementing a new system?

**GP** Education will be the main challenge that the medical community will have to overcome. It is and will continue to be difficult to show that you can move patients from unresectable state to resectable state with curative intent. The original staging, the Dukes system developed in 1932, did not mention stage 4 (Dukes D) because they had a uniformly poor prognosis. In those years, it was futile to include a stage 4 because if an individual had disease in the liver they were going to die. In the 1950s and 1960s, researchers began thinking that stage 4 was necessary, but they could not do anything for those patients because medical and surgical techniques were not fully developed. Fifty years later, we are able to

cure some of these patients in the current stage 4, but only if we educate the public and medical communities and create a staging system that has the international translatability to encourage discussion among medical experts all over the world.

**Suggested Readings**

Morris E, Thomas J, Forman D, Quirke P, Cottier B, Poston GJ. The need for a revised staging system of metastatic (M) colorectal cancer (CRC): Evidence from a national perspective on survival following surgically treated (HPX) liver metastases. *J Clin Oncol*. 2009;27(15s);abstr 4099.

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