Metastatic Colorectal Cancer: Is Surgery Necessary?

By Charlie Schmidt

Patients diagnosed with colorectal cancer can typically expect a quick trip to the operating room for tumor removal—followed, when needed, by chemotherapy. The question of when and whether to operate gets more complex if patients present with stage IV metastatic cancer, however. Colorectal metastases, which occur generally in the lungs and/or liver, leave doctors with a difficult choice: either to start with chemotherapy immediately or to remove the primary tumor first before it leads to problems, such as bleeding, perforation, or obstruction of the colon.

Now a retrospective study by surgical researchers at the Memorial Sloan–Kettering Cancer Center in New York suggests that choice shouldn’t be so difficult after all. Usually, they say, doctors who treat stage IV colorectal cancer can avoid operating. Principal investigator Philip Paty, M.D., presented the findings at the American Society of Clinical Oncology’s annual meeting in May.

“We’ve found that preemptive surgery to remove the primary tumor is almost always unnecessary,” Paty said. “In most cases, the tumor won’t progress with frontline chemotherapy and instead will probably regress. We’re not encouraging anyone to eliminate surgery as an option. But we are making the point that it doesn’t have to be done up front and that there’s nothing to lose by starting with chemotherapy first.”

Paty and his colleagues reviewed histories from 233 patients treated for stage IV colorectal cancer at Sloan–Kettering from 2000 to 2006, all treated with standard front-line chemotherapy, sometimes combined with bevacizumab, a monoclonal antibody that blocks the formation of tumor blood vessels. According to the team’s results, only 16 patients, or 7% of the cohort, developed problems from the primary tumor that called for surgical intervention. The rest never required these operations.

The finding could lead to a change in standard practice, say some experts. Now, two-thirds of all stage IV colorectal patients in the United States have their primary tumors removed as a precautionary measure, according to data gathered by Medicare and the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) program.

“If these patients don’t need the big operation, why put them through it?” asked David Rothenberger, M.D., deputy chair and professor in the department of surgery at the University of Minnesota’s Masonic Cancer Center. “The [Sloan–Kettering] study has some limitations, in that it’s retrospective, but it seems to confirm what those of us who treat these patients are already concluding: that there’s usually no sense in putting a patient through a resection of the primary lesion, particularly if it means delaying chemotherapy.”

Better Drugs Versus Surgery

Approximately 150,000 people are diagnosed annually with colorectal cancer in the United States, 20% of them with stage IV disease. For mortality, the illness ranks second only to lung cancer in men and breast cancer in women. Until the mid-1990s, only one chemotherapeutic agent was standard for treating stage IV colorectal cancer, a drug called 5-fluorouracil (5-FU), which was patented in August 1957. That drug shrank primary tumors in just 20% of patients, which may have justified surgery to remove the malignancy before it became more troublesome.

After 5-FU, the first new treatment to appear was irinotecan, which received accelerated approval from the U.S. Food and Drug Administration in June 1996 and full approval in 1998. Multidrug regimens for the illness became available soon after: oxaliplatin combined with 5-FU and leucovorin (FOLFOX), irinotecan combined with 5-FU and leucovorin (FOLFIRI), and oxaliplatin plus capcitabine (XELOX).

These multidrug regimens have been associated with substantially improved survival. Before the advent of such combinations, stage IV colorectal cancer patients had a median life expectancy of just 14 months, whereas today that figure nears 30 months, according to Scott Kopetz, M.D., assistant professor at the University of Texas M. D. Anderson Cancer Center in Houston. Moreover, 30% of stage IV patients diagnosed now can expect to live at least 5 years.

The drugs work in part by shrinking primary tumors, which lessens the likelihood for potentially lethal complications. When Paty and his colleagues saw this effect firsthand, they changed their approach for managing stage IV patients. Instead of immediately removing the primary tumor, they started with chemotherapy as standard practice. According to Leonard Saltz, M.D, one of the Sloan–Kettering investigators, surgery was offered only when patients were already obstructed, close to obstructed, or suffering from excessive bleeding. “We responded to a general notion that colorectal cancer was becoming a chemosensitive disease,” Saltz said.

Saltz emphasizes that there is now no need for surgeons to prepare patients for chemotherapy by removing their primary tumors. “That traditional practice isn’t
correct,” he said. “Patients should be sent directly to chemotherapy, because we, the chemotherapists, do not need them to be prepared for it. All the operation does is delay the start of chemotherapy, and it does not, in contrast to older thinking, make chemotherapy any safer.”

Overinterpreted?
Other experts acknowledge the benefits of sometimes using chemotherapy first, but they worry that the new findings could be overinterpreted. Robert Cima, M.D., associate professor of surgery at the Mayo Clinic in Rochester, Minn., cautions that some might see the findings as evidence to suggest that up-front surgery is never warranted. “Stage IV colorectal cancer is a multispectral disease,” Cima said. “There’s a big difference between an otherwise healthy patient who shows up with a single liver metastasis and someone who presents with the same stage IV tumor but with 15 liver metastases.” Cima said he would never tell the patient with one metastasis that he or she was not a surgical candidate. “Our approach is that if you show up with resectable disease, we should take it out and start chemotherapy later.”

Paty said he agrees that stage IV patients with easily resectable metastases can benefit from up-front surgery. Indeed, there aren’t any data to support initial surgery followed by chemotherapy over chemotherapy followed by surgery in resectable patients, he said. But removal of those metastases—not the primary tumor—should be seen as the motivation.

According to Saltz, “if you’re already taking out the metastasis, you might as well remove the primary, too. But if you intend
to treat the metastases with chemotherapy, then there's no need to operate on the primary tumor first."

Saltz' point underscores what Paty said is the study's other main conclusion: that there's no harm in waiting to operate on the primary tumor later. Paty emphasized that, usually, the primary tumor will shrink with time, making it easier to remove should doctors want to go after it with curative intent once the metastases have been dealt with.

**Changing Practice?**

Paty’s findings will probably accelerate nonsurgical approaches for managing stage IV colorectal cancer, Rothenberger said. But Nancy Baxter, M.D., associate professor at St. Michael's Hospital at the University of Toronto, said that she doesn't think the study in and of itself can change practice guidelines, which generally recommended surgical removal of the primary tumor. “They didn’t say which approach was superior—surgery or chemotherapy,” she said. “There’s a big gray zone between those who are obvious surgical candidates and those who aren’t.”

Baxter also argues that multi-institutional data are needed to avoid biases specific to any one research center. Ideally, those data would come from a randomized clinical trial comparing surgical to nonsurgical approaches. But experts concede that’s not an option with respect to stage IV colorectal cancer because patients would never agree to be randomly assigned to one treatment group over another.

Another research option is a case series. One such trial is now under way, headed by Nicholas Petrelli, M.D., medical director of the Helen F. Graham Cancer Center at Christiana Care Health System in Wilmington, Del. According to Petrelli, the trial will assess outcomes among 90 patients treated for asymptomatic colon cancer (not rectal cancer) with unresectable metastases. The chemotherapy used in this nonrandomized study can be bevacizumab combined with either FOLFOX or FOLFIRI.

The aim is to find out how many patients getting roughly the same treatment will ultimately need surgery for primary tumor complications, including bleeding, perforations, obstructions, or fistulas. The study sites are mostly community practices that belong to the NCI's Community Clinical Oncology Program.

“And that's an advantage for us,” Petrelli said. “What we’re going to see here is how community cancer surgeons deal with this issue and not necessarily the big-time university doctors.” Study recruitment is now complete and results are expected this fall.

Petrelli said that surgeons, being somewhat traditional and conservative, will stick to old approaches until they see major changes in the standard of care. Should the ongoing study replicate the Sloan-Kettering findings, he said, practice guidelines for stage IV treatment could change accordingly. “There’s still a lot of controversy out there—some surgeons will say you have to remove the primary [tumor] and some don’t,” he said. “But when you look at the SEER data, you see that most patients are still getting this surgery. This is a very practical situation, and I’m convinced our trial will give us an answer one way or another. We’d like to be able to save patients from an operation they don’t need.”