INTERVIEW

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Track 1

Case discussion

A 52-year-old man with mildly symptomatic Stage IV colon cancer and bilobar hepatic metastases receives preoperative FOLFOX/bevacizumab followed by a synchronous resection of the primary tumor and metastases.

DR GELLER: This patient was mildly symptomatic but had no bleeding or obstruction. This now presents a dilemma: What are the options for a patient who has synchronous Stage IV colon cancer and liver metastases?

One is to consider resection up front followed by chemotherapy. The second option is to administer a few cycles of chemotherapy up front, restage in three months and then perform resections. The third option is to resect the primary tumor if a hepatic surgeon is not available, then administer systemic therapy followed by a liver resection three or four months later.

We discussed this patient at a tumor board, and I favored three months of neoadjuvant FOLFOX/bevacizumab. When the primary tumor is in place, the concern is always that bevacizumab will induce bleeding, especially in rectal cancer. This man was relatively young, was not anemic and no clinical bleeding was present. In that setting, I always favor being as aggressive as possible and administer a four-drug regimen, with standard chemotherapy and a biologic agent.

In my practice, chemotherapy is discontinued three weeks prior to performing hepatic resection, and bevacizumab is held during the last cycle of chemotherapy.

The repeat imaging showed near resolution of PET activity in the primary tumor and 20 to 30 percent shrinkage in the two liver tumors. His symptoms resolved quickly, he tolerated the therapy without difficulty and we performed a synchronous resection.

The final pathology was T3N1M1, with negative margins in the colon and liver. He resumed chemotherapy with bevacizumab, which was held for the first cycle to avoid wound-healing issues. He completed his systemic treatment, and his three-, six- and nine-month scans were fine.

Tracks 3, 5

DR LOVE: In terms of determining whether liver metastases are resectable, it seems that two primary issues must be considered. First is whether a metastasis is impinging on a critical structure, such as the portal vein, and the second issue is whether, if all of the disease is removed, the patient has adequate residual hepatic function, usually requiring more than 30 percent of the liver remaining. Do you follow this paradigm?

DR GELLER: Those are both valid and important points. When I assess resectability, three issues come to mind: vascular inflow, vascular outflow and future liver remnant. Thirty percent is right on target. However, 30 percent liver remnant is much different in a 38-year-old than it is in a 70-year-old with diabetes, morbid obesity and a fatty liver. When you add chemotherapy for that older patient with comorbidities, you have to consider the quality of liver reserve — 30 percent may not be adequate.

DR LOVE: What are your thoughts about the NSABP-C-11 study?

DR GELLER: NSABP-C-11 is a Phase III clinical trial addressing the specific question of whether patients with potentially resectable hepatic colorectal cancer metastases benefit from neoadjuvant systemic therapy. We don't know the answer yet. Nordlinger's EORTC-40983 study was published in *The Lancet* in 2008 (Nordlinger 2008; [2.1]). In that multicenter trial patients were randomly assigned to either surgery alone or a "chemotherapy sandwich" approach consisting of three months of up-front chemotherapy followed by liver resection and then three months of adjuvant chemotherapy. This study did not address the specific benefits of the neoadjuvant therapy.

In the NSABP-C-11 study patients with resectable liver metastases are randomly assigned to surgery followed by systemic therapy or neoadjuvant therapy, liver resection and chemotherapy (2.2).

2.1

Trial Evaluating the Benefit of Perioperative FOLFOX4 for Patients with Potentially Resectable Colorectal Cancer Hepatic Metastases

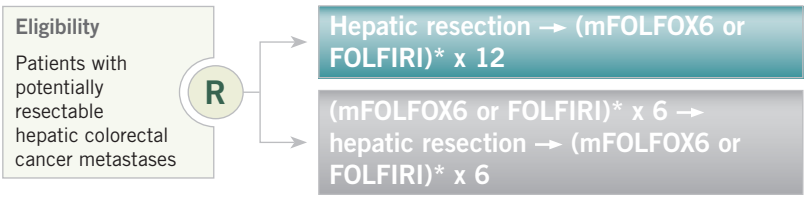
	Perioperative FOLFOX4 + surgery	Surgery alone	Hazard ratio	*p*-value
Three-year progression-free survival All patients randomly assigned (n = 182, 182)	35.4%	28.1%	0.79	0.058
All patients who underwent resection (n = 151, 152)	42.4%	33.2%	0.73	0.025
Reversible postoperative complications (n = 159, 170)	25%	16%	—	0.04
Postoperative death (n = 159, 170)	1%	1%	—	—

Nordlinger B et al. *Lancet* 2008;371(9617):1007-16.

2.2

Phase III Study Evaluating the Role of Perioperative Chemotherapy for Patients with Potentially Resectable Hepatic Colorectal Cancer Metastases

Protocol ID: NSABP-C-11 **Accrual:** 670 (Open)



* Dependent upon prior exposure to oxaliplatin

NOTE: Protocol amended to no longer include bevacizumab in combination with chemotherapy

NSABP Protocol Summaries, March 3, 2011.

Track 13

DR LOVE: What is your perception of the role of sorafenib in hepatocellular carcinoma (HCC)?

DR GELLER: Medical oncologists are using sorafenib frequently now for HCC. Five years ago we had no real systemic chemotherapies that showed promise in HCC, but it's important to realize that sorafenib is not a "wonder drug." In the SHARP trial, 602 patients received either sorafenib or placebo, and the data were humbling in that the survival benefit was about three months (2.3). That being said, it's important that sorafenib was approved because it opens the door for clinical trials with combination therapies.

We recently completed an adjuvant trial of sorafenib after surgical resection or local ablation, and we expect to see those data presented in the next year (2.4). Can we now administer sorafenib after resection or ablation, and does that improve survival? Can we combine it with chemoembolization or with yttrium-90? It's an exciting era. Even though no single agent is a "wonder drug," some of the best results in colon cancer occur when we combine three and four drugs, such as adding bevacizumab and/or cetuximab to the standard front-line chemotherapy. Now we're seeing that same approach for HCC. ■

2.3

SHARP Trial: Sorafenib in Advanced Hepatocellular Carcinoma

	Sorafenib (n = 299)	Placebo (n = 303)	Hazard ratio	*p*-value
Median overall survival	10.7 mo	7.9 mo	0.69	<0.001
Median time to radiologic progression	5.5 mo	2.8 mo	0.58	<0.001
Overall response rate	2%	1%	—	0.05

Llovet JM et al. *N Engl J Med* 2008;359(4):378-90.

2.4

Phase III Study of Sorafenib as Adjuvant Treatment for Hepatocellular Carcinoma

Protocol IDs: STORM, NCT00692770 **Accrual:** 1,115 (Closed)

www.clinicaltrials.gov, May 2011.

SELECT PUBLICATION

Nordlinger B et al. **Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): A randomised controlled trial.** *Lancet* 2008;371(9617):1007-16.