

# The OncoSurge® Decision Model

A Tool for Improving Resectability of Colorectal Liver Metastases with

## In Brief

*Increasingly, management of colorectal liver metastases includes sequenced multiple treatments involving chemotherapy, liver resection, and possibly local ablation therapies. The OncoSurge® appropriateness study was designed to assess multiple treatment strategies and present these in a manner accessible to oncologists. The OncoSurge® Decision Model, a decision matrix in the form of a computer program, allows physicians to enter a patient's clinical characteristics followed by the proposed treatment plan and then compare the treatment proposal with the OncoSurge study panel's expert recommendation.*

**C**olorectal cancer is the third most common cancer-related cause of death in the United States.<sup>1</sup> Fifteen to 25 percent of patients with colorectal cancer present with liver metastases. In patients who go on to develop metastatic disease, the liver will be involved in 50 to 75 percent of cases, although in 20 to 35 percent of patients the metastases will be confined to the liver.<sup>2</sup>

For patients with liver-only metastases, liver resection is the only treatment that offers long-term survival and the possibility of cure, with 25 to 40 percent of patients surviving 5 years and approximately 24 percent remaining alive at 10 years.<sup>3-5</sup> Historically, liver resection was only considered appropriate for patients with:

- 1 to 3 unilobar metastases
- A tumor that was detected metachronously from the resection of the primary colorectal tumor
- A tumor that was resectable with a 1 cm margin of healthy liver tissue.

Under this definition of resectability, liver resection is limited to less than 10 percent of patients with colorectal liver metastases; however, recent long-term survival data following resection of colorectal liver metastases has led to a revision of the criteria for resection (see Table 1).<sup>6</sup>

According to current criteria, about 20 percent of patients with colorectal liver metastases are suitable for resection. The major improvement in this number is now possible with the use of chemotherapeutic regimens based on 5-FU/leucovorin with oxaliplatin and/or irinotecan to convert initially inoperable patients to resectability with curative intent.

In 1996 Bismuth reported on the treatment of 872 patients with colorectal liver metastases of whom 171 (19

percent) were resectable with curative intent at presentation. The remaining 701 unresectable patients received chronomodulated oxaliplatin (25mg/m<sup>2</sup>/day) combined with 5-FU/leucovorin. Of these patients, 95 (13.6 percent) achieved a response to chemotherapy sufficient to be considered for resection. Therefore, the overall resection rate exceeded 30 percent. Of the patients who were brought to resection by chemotherapy, 34 (39 percent) were alive at 5 years post-resection and 19 (22 percent) were disease free.<sup>7,8</sup>

In a North Central Cancer Treatment Group study, 14 out of 44 patients with unresectable liver-only metastases treated with the FOLFOX-4 regimen (85mg/m<sup>2</sup> dose of oxaliplatin and high-dose continuous 5-FU/leucovorin) achieved sufficient tumor shrinkage to permit complete resection—a 31 percent resectability rate.<sup>9</sup>

In a similar study of 151 patients with initially unresectable metastatic colorectal cancer confined to the liver, treatment with chronomodulated oxaliplatin plus 5-FU/leucovorin resulted in 77 (51 percent) undergoing surgery, with complete resection achieved in 58 patients (38 percent).<sup>10</sup> Median survival of these 77 patients was 48.8 months; 5-year survival was 50 percent and 7-year survival was 30 percent.<sup>10</sup>

Lastly, a crossover trial compared an oxaliplatin-based regimen (FOLFOX-6) to an irinotecan-based regimen (FOLFIRI) in first-line therapy in 222 non-resectable patients.<sup>11</sup> In this trial, 24 patients (22 percent) who received FOLFOX-6 as the first-line therapy achieved sufficient tumor response to be considered suitable for liver resection, and complete resection was achieved in 13 patients (12 percent).<sup>11</sup>

Overall, following aggressive treatment with high-dose continuous infusion 5-FU/leucovorin plus oxaliplatin at a dose of 85mg/m<sup>2</sup> or higher, resectability rates of approximately 40 percent appear to be possible. Furthermore, long-term survival rates are comparable to those of primarily resected patients.

## Sequenced Multiple Treatments

The management of colorectal liver metastases increasingly involves a strategy of sequenced multiple treatments involving chemotherapy, liver resection, and possibly local ablation therapies.<sup>12</sup> When planning such sequenced treatment strategies, healthcare providers must keep in mind that the application of each sequenced treatment is dependent on the success, or otherwise, of the preceding treatment sequence. For example, in a patient with multiple bilobar colorectal liver metastases, including an 8 cm metastasis close to the vena cava, and a possible small (and potentially resectable) single lung metastasis, any intention to resect and/or ablate the liver disease (with subsequent

**Table 1. Current Criteria for Resection of Colorectal Liver Metastases**

Patient and Tumor Characteristics	Eligibility Criteria for Resection
Age	Dependent on co-morbidity and performance status rather than age per-se
Number of metastases	No maximum number. Poorer prognosis with > 3 metastases, but may still benefit from surgery
Bilobar metastases	Not a barrier to resection
Size of metastases	No upper limit on size. Some report poorer prognosis with larger tumors, but may still benefit
Synchronous detection of colorectal primary and liver metastases	Not a contra-indication
Dukes Staging of colorectal primary	Dukes A and B. Poorer prognosis with Dukes C, but may still benefit
Liver resection margin	1 to 2 mm resection margin may be acceptable
Extra-hepatic metastases	Liver resection contra-indicated, unless resectable isolated lung metastases, resectable adrenal gland metastases, and direct diaphragmatic invasion

lung resection) should be dependent on the success—or otherwise—of prior neoadjuvant chemotherapy.

### The OncoSurge Study

The OncoSurge appropriateness study was designed to assist physicians in the management of patients with colorectal liver metastases. The study uses present knowledge (based on the RAND/UCLA Appropriateness Method (RAM)<sup>13, 14</sup>) to assess multiple treatment strategies. Results are then presented in a manner accessible to “typical” care providers.

An international expert panel of 16 surgeons, medical oncologists, and radiologists from North America and Europe participated in the study. Three treatment segments were considered: surgical resection of the liver, local ablation, and chemotherapy.

When the panel first convened in August 2003, data on biologic therapies were only just appearing and were not approved for use in the U.S. at that time. Within each treatment segment, the decision model distinguished between a number of different treatment options (see Table 2).

During its first meeting, the panel discussed state-of-the-art treatment for liver metastases aided by a recent systematic literature review prepared specifically for this purpose. All possible patient characteristics likely to influence treatment of metastatic liver disease were identified. Although age, stage of primary tumor, timing of detection of metastases, blood transfusion, type of resec-

tion, pre-surgical CEA, and previous liver resection are known to be prognostic factors for survival,<sup>4,15</sup> the panel agreed that they would not radically influence the treatment strategies. Absolute contra-indications to surgery were agreed upon:

- Extensive metastases (portal nodal involvement, peritoneal, multi-focal lung, Virchow’s nodes, bone or brain)
- Extensive liver involvement (>6 segments involved, > 70 percent tumor invasion of the liver, all 3 hepatic veins involved)
- Major liver insufficiency; Child’s B or C liver cirrhosis with complications
- Inability to tolerate the procedure
- Patient declines procedure.

For each of the three treatment segments, the RAM was applied to a combination of patient characteristics and segmental treatment options. The RAM is a statistically validated method that is a modified Delphi process.<sup>13,14</sup>

In total 1,872 combinations were considered. The panel rated the appropriateness of each combination on a scale of 1 to 9, where 1 to 3 indicated “inappropriate” (harm of treatment outweighs the benefits), and 7 to 9 indicated “appropriate” (benefits outweigh the harm). A rating of 4 to 6 indicated “uncertain” (benefits and harm are about equal or panel members disagree).

Analysis of appropriateness was on the strategies as a whole, not on the different tactics employed by the sur-

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geons or oncologists for implementing the strategies. The different treatment strategies that resulted from the second round of ratings were then incorporated into a decision matrix in the form of a computer program—the OncoSurge® Decision Model.

**Construction of the Decision Model**

The decision model was constructed using a classification tree analysis with a risk <5 percent. The results were validated on 48 hypothetical clinical cases. To test the range of agreement/disagreement within the final ratings of the panel, these hypothetical cases were specifically constructed to cover all possible variables for clinical presentation of colorectal liver metastases. When validated, there was agreement in 47 out of 48 cases for resection and chemotherapy, and in 42 out of 48 for local destruction. Finally, the panel compared its ratings using 34 real cases with known outcomes, which were brought to the second meeting by the individual panelists. Agreement between the panelists after the second round of ratings ranged between 93.4 to 99.1 percent.

**Liver resection.** Immediate liver resection was considered appropriate when the liver surgeon and radiologist agreed that the pre-operative CT scan showed adequate proposed surgical resection margins, absence of suspiciously enlarged portal lymph nodes, and ≤4 metastases with either uni- or bilobar liver involvement or >4 but confined to only one lobe of the liver.

Resection after pre-operative chemotherapy, independent of tumor response, was appropriate if the number of metastases was >4 and there was unilobar

involvement, and also in the presence of resectable extra-hepatic disease. If the number of metastases was >4 with bilobar involvement, even if amenable to tri-segmentectomy, resection was only appropriate

if there was evidence of tumor volume reduction after pre-operative chemotherapy.

Liver resection in the presence of radiologically suspicious portal lymph nodes was only appropriate if there was radiologic evidence of resolution of these nodes after pre-operative chemotherapy.

**Local ablative therapy.** The panel agreed that there were few appropriate indications for local ablative therapy, and resection was always preferred if possible. Indications included a patient unfit for surgery with ≤4 small metastases. Ablation could be utilized with resection if >4 metastases were present.

**Chemotherapy.** Chemotherapy with 5-FU and LV was rated as inappropriate in all clinical situations (pre-, with neoadjuvant and/or down-staging intent, and post-operative, and also for palliation). The three regimens using 5-FU/LV combined with oxaliplatin and/or irinotecan were generally appropriate, except in the case of complete resection where the benefit of post-operative adjuvant chemotherapy was regarded as uncertain. Since more published data existed on the use of peri-operative oxaliplatin-based regimens, the combination of 5-FU/LV with oxaliplatin was rated slightly higher than treatment with irinotecan. Because the triple therapy of 5-FU/LV with oxaliplatin and irinotecan is not an approved indication in any part of the world for the treatment of colorectal liver metastases, the appropriateness of its use was

**Table 2. Treatment Options for Each Segment of the OncoSurge® Decision Model**

Resection	Local destruction	Chemotherapy
No resection	Local destruction together with resection	5-FU/LV
Immediate resection	Local destruction instead of resection, if resection is contra-indicated for any reason	5-FU/LV + oxaliplatin
Resection after pre-operative chemotherapy		5-FU/LV + irinotecan
Resection after pre-operative chemotherapy only if tumor shrinkage is achieved		5-FU/LV + oxaliplatin + irinotecan

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restricted to incomplete resections.

Recently, however, the panel has agreed that the pragmatic approach to chemotherapy in the peri-operative setting is to recommend “dealer’s choice” to the local oncologist, thus allowing the use of hepatic arterial infusional and the newly available biologic therapies.

The OncoSurge® Decision Model is now available free of charge on CD-ROM, and by late summer 2005 the decision model should also be available on the Internet. The model is intended for general and colorectal surgeons (non-hepatobiliary specialists) and oncologists, to assist in optimizing the management of patients with colorectal liver metastases.

To use the OncoSurge® Decision Model, physicians enter an individual patient’s clinical characteristics followed by the proposed treatment plan and then compare their treatment proposals with the expert recommendation. Alternatively, the program also allows physicians in a busy clinic or tumor board immediate access to the panel recommendations on the treatment strategies for their patient.

The OncoSurge program contains the 34 real clinical cases, complete with CT scans, used by the expert panel in its second meeting. Lastly, the CD-ROM contains the bibliography of the systematic review (in abstract form) relating to prognostic factors and treatment strategies that was used by the OncoSurge panel of experts.

While the OncoSurge® Decision Model may provide useful guidance in improving the management of patients with colorectal liver metastases—in particular increasing the number who are eligible for potentially curative resection—keep in mind that the definition of “appropriate care” very much depends on local circumstances and resources, as well as the preferences of patients and families. 

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