Perioperative Carcinoembryonic Antigen Measurements to Predict Curability After Liver Resection for Colorectal Metastases

A Prospective Study

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Hypothesis: Perioperative carcinoembryonic antigen (CEA) blood level is a predictor of outcome after resection of colorectal liver metastases (CLMs).

Design: Prospective clinical study.

Setting: Department of digestive surgery and transplantation.

Patients: Between January 1, 2000, and December 31, 2004, CEA levels were routinely measured 1 week before and 6 weeks after CLM resection in 213 patients. The patients were divided into the following 3 groups: group A (n=69) with normal preoperative and postoperative CEA levels, group B (n=111) with elevated preoperative and normal postoperative CEA levels, and group C (n=33) with elevated preoperative and postoperative CEA levels.

Main Outcome Measures: The use of perioperative CEA levels to predict outcome after resection.

Results: The median survival was 45.4 months. The 5-year overall and disease-free survival rates were 50.2% and 21.9%, respectively, in group A, 38.5% and 18.3% in group B, and 0.0% and 0.0% in group C (P<.001). Univariate analysis showed that patients with elevated preoperative and postoperative CEA levels, multiple CLMs, large CLMs (≥5 cm), advanced Fong clinical risk score, bilobar distribution, and hepatic pedicle lymph node involvement had significantly poorer overall and disease-free survival. By multivariate analysis, only perioperative CEA level, hepatic pedicle lymph node involvement, and number and size of CLMs were independent prognostic factors. The 5-year survival rates showed good correlation with perioperative CEA levels in all 3 patient groups.

Conclusions: The predictive value of perioperative CEA levels is demonstrated. Carcinoembryonic antigen levels as early as 6 weeks after surgery may be helpful in assigning patients to adjuvant chemotherapy after resection of CLMs.
METHODS

STUDY DESIGN

During the study period, preoperative and postoperative CEA levels were measured according to an established protocol and were collected prospectively. The preoperative CEA measurement was performed within 1 week before liver resection. Blood samples for postoperative CEA measurement were obtained 6 weeks after liver resection during a short hospitalization scheduled for removal of a transcystic biliary drain routinely placed at the time of liver resection. Both CEA measurements were performed in our hospital laboratory using an electrochemiluminescence immunoassay (Elecsys 2010; Roche Diagnostics GmbH, Mannheim, Germany). A normal CEA level defined by this test is less than 5.0 ng/mL (to convert CEA level to micrograms per liter, multiply by 1.0). Patients who underwent noncurative liver resection (ie, grossly incomplete liver resection or complete resection with persistent extrahepatic disease) were excluded from this study. Patients in whom complete resection of all known extrahepatic disease was achieved at the time of liver resection were included. In patients who underwent planned 2-stage hepatectomy, only preoperative and postoperative CEA levels corresponding to the second liver resection were analyzed. The criteria for performance of preoperative portal vein embolization or staged hepatectomy (1-stage or 2-stage) were previously described. Briefly, they concern patients with initially unresectable liver metastases (ie, multiple bilobar or small future remnant liver). Major liver resection was considered when at least 3 contiguous liver segments (as defined by Couinaud) or 2 segments of the hepatic dome were resected. The decision to perform hepatic lymph node dissection was based on prognostic factors described in a previous prospective study.

STUDY POPULATION

Between January 1, 2000, and December 31, 2004, 233 patients were operated on for CLMs. Of these, 215 patients underwent curative R0 liver resection, defined as complete and incomplete resection of all known extrahepatic disease was achieved at the time of liver resection. Of these, 215 patients underwent planned 2-stage hepatectomy, only preoperative and postoperative CEA levels corresponding to the second liver resection were analyzed. The criteria for performance of preoperative portal vein embolization or staged hepatectomy (1-stage or 2-stage) were previously described. Briefly, they concern patients with initially unresectable liver metastases (ie, multiple bilobar or small future remnant liver). Major liver resection was considered when at least 3 contiguous liver segments (as defined by Couinaud) or 2 segments of the hepatic dome were resected. The decision to perform hepatic lymph node dissection was based on prognostic factors described in a previous prospective study.

ADJUVANT AND NEOADJUVANT CHEMOTHERAPY

Patients who had undergone adjuvant chemotherapy were referred to our department for further treatment planning. Among them, 23 patients (13.2%) had normal CEA levels and were assigned to group A. The decision to give additional adjuvant therapy was made after receiving final pathologic examination results in a multidisciplinary conference that included oncologists, gastroenterologists, radiologists, and surgeons. A change in CEA level from before to 6 weeks after liver resection was not considered in the decision to give adjuvant therapy in these patients. Patients treated with neo-

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The mean (SD) CA 19-9 level was 31.4 (69.5) U/mL (range, 1-402 U/mL).

CHARACTERISTICS OF LIVER METASTASES

Colorectal liver metastases were metachronous in 107 patients (50.2%) and bilobar in 90 patients (42.3%) (Table 1). The mean (SD) size of the largest liver metastases was 46.8 (27.4) mm (range, 15-160 mm). The mean (SD) interval between primary tumor resection and liver resection was 21.6 (17.8) months (range, 3-96 months). Eighty-two patients had solitary liver metastases, 36 had 2 metastases, 36 had 3 metastases, and 59 had more than 3 metastases.

ASSOCIATED PROCEDURES

Twenty-seven patients underwent associated procedures at the time of hepatectomy. These included resection of colorectal primary tumors (n=12), resection of solitary peritoneal implants (n=12), partial diaphragmatic resection (n=2), and right adrenal gland resection (n=1). Hepatic pedicle and retroduodenopancreatic lymph node dissection was performed in 132 patients. Among them, 12 patients (9.1%) had microscopic hepatic pedicle lymph node metastases discovered at pathologic examination. No patient had macroscopic evidence of hepatic pedicle lymph node involvement.

COMPARABILITY OF THE STUDY GROUPS

The 3 study groups were similar in age, sex, primary tumor site, pTNM stage, type and topography of liver metastases, disease-free interval between primary tumor resection and diagnosis of liver metastases, number of liver metastases, size of largest liver metastases, presence of resectable solitary peritoneal implant, hepatic pedicle lymph node involvement, and neoadjuvant and adjuvant chemotherapy regimens. However, preoperative portal vein embolization was significantly more frequent in group C (39.4% [13 of 33 patients]) than in group A (15.9% [11 of 69 patients]) or group B (27.9% [31 of 111 patients]) (P=.03).

SURGICAL DATA

Major hepatectomy was performed in 98 patients. Preoperative right portal vein embolization was performed in 55 patients (28 before planned 1-stage hepatectomy and 27 before planned 2-stage hepatectomy). Liver resections included 47 bisegmentectomies (10 requiring additional subsegmental metastasectomies), 32 right hepatectomies (3 requiring additional metastasectomies in the left lobe), 23 extended right hepatectomies (7 requiring additional metastasectomies in the left lateral lobe), 5 left hepatectomies (1 requiring an additional metastasectomy), 2 extended left hepatectomies, 16 left lobectomies (13 requiring additional metastasectomies in the right lobe), 53 unisegmentectomies (18 requiring additional metastasectomies), 7 trisegmentectomies (1 requiring left lobectomy and 1 requiring an additional metastasectomy), and 28 subsegmental metastasectomies.

ADJUVANT CHEMOTHERAPY AFTER LIVER RESECTION

Adjuvant chemotherapy regimens included the following: fluorouracil plus folinic acid in 73 patients, fluorouracil plus folinic acid and oxaliplatin in 67 patients, and fluorouracil plus folinic acid and irinotecan in 38 patients.

PATIENTS UNDERGOING 1-STAGE OR 2-STAGE HEPATECTOMY WITH PORTAL VEIN EMBOLIZATION

The 1-year, 3-year, and 5-year overall survival rates in 55 patients who underwent staged hepatectomy (90.9%, 56.5%, and 29.4%, respectively) were similar to those in 158 patients who did not undergo staged hepatectomy (92.4%, 69.8%, and 38.4%, respectively) (P=.09). Moreover, the perioperative change in CEA level significantly predicted survival in patients undergoing staged hepatectomy combined with portal vein embolization (Figure 1 and Figure 2). Finally, the 5-year survival rate was significantly lower in patients undergoing 2-stage hepatectomy for initially nonresectable disease (18.9%) compared with that in patients with initially resectable liver metastases (38.4%) (P=.02).

LONG-TERM OUTCOMES

The mean (SD) follow-up after hepatectomy was 34.7 (17.2) months (range, 3.1-78.5 months). Among 114 surviving patients (53.5%), 64 patients were recurrence free after a mean (SD) follow-up of 37.0 (16.5) months (range, 10.3-78.5 months). Fifty patients had recurrences after a mean (SD) follow-up of 44.6 (17.1) months (range, 20.0-77.4 months). The remaining 99 patients (46.5%) died after a mean (SD) follow-up of 28.1 (14.9) months (range, 3.1-66.3 months) after hepatectomy. Death was directly related to cancer relapse except in 2 patients, one with cardiac infarction 34.2 months after hepatectomy and the other with head and neck cancer 22.7 months after hepatectomy. Recurrences included the following: liver (n=72), lung (n=57), peritoneum (n=14), bone (n=10), primary tumor site (n=9), disseminated disease (n=9), retroperitoneal lymph nodes (n=6), brain (n=3), adrenal glands (n=1), and ovary (n=1). Perioperative change in CEA level did not correlate with site of recurrence. The overall median survival was 45.4 months. The 1-year, 3-year, and 5-year overall survival rates were 92.0%, 66.3%, and 35.8%, respectively. Disease-free survival rates were 74.1%, 32.3%, and 17.7% at 1 year, 3 years, and 5 years, respectively.

ANALYSIS OF PROGNOSTIC FACTORS FOR SURVIVAL

Univariate analysis showed that the status of hepatic pedicle lymph nodes, CEA level 6 weeks after hepatectomy (P < .001), perioperative change in CEA level, and number, size, and distribution of liver metastases were
<table>
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<tr>
<th>Variable</th>
<th>Overall Survival, %</th>
<th>Disease-Free Survival, %</th>
<th>P Value</th>
<th>P Value</th>
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<td></td>
<td>3-y</td>
<td>5-y</td>
<td>3-y</td>
<td>5-y</td>
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<td>Age, y</td>
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<td>Hepatic pedicle lymph node involvementc</td>
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<td>29.4</td>
<td>18.9</td>
<td>12.6</td>
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<td>Perioperative CEA level change</td>
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<td>50.2</td>
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<td>Group B (n=111)</td>
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<td>Group C (n=33)</td>
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</table>

Abbreviation: CEA, carcinoembryonic antigen.

SI conversion factor: To convert CEA level to micrograms per liter, multiply by 1.0.

a One patient whose primary tumor (in situ adenocarcinoma) was resected during colonoscopy had unknown lymph node status.

b Data were available for 208 patients in whom CEA levels were measured before the beginning of neoadjuvant chemotherapy.

c Data available for 132 patients in whom hepatic pedicle lymph node dissection was performed.

d Group A had normal preoperative and postoperative CEA levels, group B had elevated preoperative and normal postoperative CEA levels, and group C had elevated preoperative and postoperative CEA levels. For overall survival, significant differences were observed between group A and group C and between group B and group C (P<.001 for both). No significant difference was observed between group A and group B (P=.53). For disease-free survival, significant differences were observed between group A and group C and between group B and group C (P<.001 for both). No difference was observed between group A and group B (P=.34).
significant prognostic factors of overall survival and disease-free survival (Table 1). Analyzed as a continuous variable, the CEA level 6 weeks after hepatectomy also affects survival ($P < .001$). The primary tumor lymph node status, disease-free interval between primary tumor resection and diagnosis of liver metastases, CEA level before hepatectomy ($< 200 \text{ vs } \geq 200 \text{ ng/mL}$), and CEA level before neoadjuvant chemotherapy (normal vs abnormal) did not reach statistical significance ($P = .06$). Finally, the CEA level before hepatectomy (normal vs abnormal, $P = .19$) and the CEA level before neoadjuvant chemotherapy ($< 200 \text{ vs } \geq 200 \text{ ng/mL}, P = .94$) did not affect survival.

Analysis of the change in CEA level during neoadjuvant chemotherapy was performed by excluding patients with normal CEA levels before and after chemotherapy. The remaining 156 patients who received neoadjuvant chemotherapy were divided into the following 2 groups: group 1 comprising 49 patients with an increase in CEA level after completion of chemotherapy and group 2 comprising 107 patients with a stable CEA level or a decrease in CEA level after completion of chemotherapy. Univariate analysis showed that change in CEA level after neoadjuvant chemotherapy was also a predictor of overall survival (1-year, 3-year, and 5-year overall survival rates, respectively, were 91.8%, 54.7%, and 19.3% in group 1 vs 90.7%, 67.3%, and 34.9% in group 2; $P = .048$). However, disease-free survival was unaffected by change in CEA level after neoadjuvant chemotherapy (1-year, 3-year, and 5-year disease-free survival rates, respectively, were 69.3%, 12.7%, and 8.4% in group 1 vs 69.2%, 30.6%, and 16.4% in group 2; $P = .12$).

In group A patients, the preoperative CA 19-9 level did not affect survival (4-year survival, 56.6% for patients having normal vs 46.9% for patients having abnormal levels; $P = .17$). Patients having recurrence with an increased CEA level had similar survival vs those having recurrence with a normal CEA level (5-year survival, 28.8% vs 36.5%; $P = .27$).

In multivariate analysis, perioperative change in CEA level, hepatic pedicle lymph node metastases, and number and size of liver metastases were significant and independent prognostic factors for overall and disease-free survival (Table 2). In addition, sex was a significant prognostic indicator for disease-free survival.

The clinical risk score proposed by Fong et al. for prediction of long-term outcomes after liver resection of CLMs was validated in the present series. Our study population was divided into the following 3 groups: 44 patients with a clinical risk score of 0 to 1, 135 patients with a clinical risk score of 2 to 3, and 34 patients with a clinical risk score of 4 to 5. As expected, patients with a clini-

**Table 2. Multivariate Cox Proportional Hazards Regression Analysis of Prognostic Factors for Long-term Outcomes**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Relative Risk (95% Confidence Interval)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perioperative change in CEA level in group C vs groups A and B</td>
<td>3.0 (1.4-6.3)</td>
<td>.003</td>
</tr>
<tr>
<td>Multiple vs single liver metastases</td>
<td>2.0 (1.2-3.3)</td>
<td>.008</td>
</tr>
<tr>
<td>Largest liver metastases $\geq 5 \text{ vs } &lt; 5 \text{ cm}$</td>
<td>1.9 (1.1-3.1)</td>
<td>.02</td>
</tr>
<tr>
<td>Hepatic pedicle lymph nodes invaded vs not invaded</td>
<td>3.9 (1.9-8.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Male vs female sex</td>
<td>2.4 (1.2-4.6)</td>
<td>.01</td>
</tr>
</tbody>
</table>

*Abbreviation: CEA, carcinoembryonic antigen.*
The present prospective study demonstrates that postoperative CEA measurement, particularly preoperative and postoperative CEA levels after CLM resection, is a significant prognostic factor for overall and disease-free survival. Furthermore, normalization of CEA levels 6 weeks after CLM resection may indicate improved long-term outcomes in these patients.

Numerous tumor markers have been described to assess patients with colorectal cancer, including levels of p53, CEA, cytokeratin, vascular endothelial growth factor, and CAs such as CA 19-9, CA 242, and CA 72-4. Among these markers, CEA level remains the most widely used. For colorectal cancer, the prognostic value of preoperative CEA measurement was highlighted by several studies. Other studies demonstrated the benefit of systematic postoperative CEA monitoring to diagnose early recurrence after resection or to assess response to chemotherapy in patients with CLMs. However, few studies have studied the usefulness of perioperative changes in CEA level for evaluating the success of surgical resection (ie, whether a presumed complete resection as defined by intraoperative and pathologic findings is effectively curative). The present study shows that patients with elevation of both preoperative and postoperative CEA levels have significantly lower median survival (28.3 months for group C) compared with patients with normal postoperative CEA levels (53.8 months for group A and 45.5 months for group B), indicating that postoperative CEA levels can be used as a marker for complete vs incomplete (cytoreductive) surgery. Therefore, patients with elevated postoperative CEA levels are particularly vulnerable to recurrence and should be considered for additional treatment. Finally, in the present series, the finding of the worst prognosis in patients
requiring 2-stage hepatectomy was related to the pre-
dominance of these patients in group C. In fact, because of their higher disease burden, they are at higher risk of noncurative resection, as reflected by higher elevated post-
aperative CEA levels and worse outcomes. However, in selected patients, planned 2-stage hepatectomy remains the only surgical option that offers patients a chance of long-term survival.

The potential clinical value of preoperative and post-
aperative CEA levels was underscored several years ago by Hohenberger et al. They demonstrated that postoperative CEA level was the most important predictive factor for overall and disease-free survival among 141 pa-
tients who underwent R0 resection for CLMs. They suggested that CEA level was the best criterion to judge whether curative resection has been performed. How-
ever, their study included only patients with unilobar resectable disease and no more than 3 liver metastases. Moreover, data about chemotherapy were not reported. It is notable that preoperative vs postoperative change in CEA level remained the most powerful predictor of long-term outcomes in the present series, which included patients with more advanced metastatic disease such as multiple and bilobar metastases, patients with ini-
tially nonresectable disease, and patients requiring staged hepatectomy combined with portal vein embolization.

The clinical risk score developed by Fong et al11 and validated by Mann et al12 was also predictive of outcome and survival in the present series. In our study, persist-
ten elevated postoperative CEA levels after CLM resec-
tion identified a subgroup of patients with the worst prog-
nosis. This was particularly true for patients with a clinical risk score of 2 to 3. The clinical risk score is based on 5 static preoperative variables and evaluates disease sta-
tus before CLM resection. The inclusion of postopera-
tive CEA measurement allows assessment of tumor be-
havior in sequence, particularly in patients with elevated preoperative CEA levels. This measurement better iden-
tifies those patients with the best chance for cure after metastasectomy. For patients with normal preoperative CEA levels, the clinical risk score is the only good prog-
nostic tool available because CA 19-9 is of no prognostic-
tic value in this situation, as shown by the present study and in a previous study by Weber et al.13

The reported rates of normal preoperative CEA lev-
els in patients with CLM range from 16% to 35.1%.22,52 In a previous study13 of patients with CLMs operated on be-
tween 1988 and 1998, the percentage of patients with normal preoperative CEA levels was 19.5% (43 of 221 pa-
tients). At that time, patients received neither oxali-
patin- nor irinotecan-based chemotherapy regimens. Therefore, in the present series, the wide range in the rates of patients with normal preoperative CEA levels could be explained by the effect of neoadjuvant chemotherapy on preoperative CEA levels. Indeed, 69 patients (32.4%) (group A) had normal preoperative CEA levels. This rate is an overestimation of patients not expressing CEA be-
cause 174 study patients (81.7%) received neoadjuvant chemotherapy, which led to a normalization of CEA lev-
els in 23 patients (13.2%).

Several previous studies reported the usefulness of mea-
suring changes in CEA level after complete tumor resec-
tion. The reported median half-life of CEA is 4 days (range, 1-88 days).50,53 This suggests that premature measure-
ment of postoperative CEA levels may overestimate the number of patients with persistent CEA level elevation. Con-
versely, it has been demonstrated that prolonged CEA half-lives are often associated with the existence of over-
looked synchronous metastases.33 We chose a 6-week in-
terval for postoperative CEA measurements because we found that it accurately identified patients with persist-
tent CEA level elevation without delaying the initiation of adjuvant chemotherapy. These arguments were suf-
cient for us to stop routine early postoperative CEA mea-
surements after liver resection.

Carcinoembryonic antigen levels are an established prog-
nostic indicator for monitoring disease progression and for early detection of recurrence.32,46-51 The present series demonstrated better prognosis for patients hav-
ing normal preoperative CEA levels compared with pa-
tients having elevated preoperative and postoperative CEA levels. However, the survival rates were similar in both groups of patients with normal postoperative CEA lev-
els (groups A and B). There is no evidence that CEA-
producing CLMs have more aggressive behavior than non-
CEA-producing CLMs. Indeed, the primary tumor and CLM characteristics were similarly distributed in the 3 groups of patients. This study demonstrates that persist-
ently elevated postoperative CEA levels indicate the pres-
ence of unidentified residual disease, with subsequent poor prognosis and increased risk of relapse. In this series, post-
aperative CEA measurements in patients with elevated preoperative CEA levels were useful in predicting ultimate surgical failure after intent-to-cure CLM resec-
tion. Elevated CEA levels in the immediate postopera-
tive period can identify the subgroup of patients with clinically undetectable residual disease who will benefit from postoperative chemotherapy. In these patients, post-
aperative chemotherapy should be regarded as therapeutic rather than as adjuvant. Elevated CEA levels in the early postoperative period are not used as an indication for surgical intervention.

Most series about CLMs have reported various prog-
nostic scoring systems based on different prognostic fac-
tors.3,4,10,17,22,24,54 All of them are useful in selecting pa-
tients for surgery and for predicting their outcomes. How-
ever, the major concern today is to better define the radicality of potentially curative resection rather than to identify patients at risk of recurrence. More efficient che-
motherapy, multimodality treatment approaches, and in-
novation in surgical strategies (2-stage hepatectomy, port-
al vein embolization, and radiofrequency ablation) have increased the numbers of patients con-
sidered for liver resection and more frequently include patients initially considered as having nonresectable dis-
case. The present study demonstrates the use of com-
bined preoperative and postoperative CEA measure-
ments to identify patients who had incomplete resection in the setting of intent-to-cure metastasectomy for col-
rectal cancer. This study also shows that postoperative CEA measurements are of limited prognostic value in pa-
tients with normal preoperative CEA levels.

In conclusion, preoperative CEA measurement is a well-recognized prognostic factor. This study demon-
strates that it is not a good predictor of postoperative outcome or of biologic aggressiveness of the disease. Preoperative CEA measurement did not predict performance of complete resection, nor did it accurately predict postoperative disease progression. However, our study showed that postoperative CEA level 6 weeks after CLM resection and its normalization represent the most reliable predictive criteria for complete and successful hepatic metastasectomy.

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36. Kim SB, Fernandez LC, Saad SS, Matos D. Assessment of the value of preop-
epatic resection is the only curative option for patients with hepatic metastases from colorectal cancer (CRC). Five-year survival rates after resection have reached almost 60% in recent series.\(^1\)\(^-\)\(^3\)

This is largely attributed to more sophisticated preoperative imaging techniques, highly sensitive intraoperative ultrasonographic detection of small metastases, improved surgical techniques, and more effective systemic therapies.\(^4\)\(^-\)\(^9\)

Improved survival and decreased mortality for patients with hepatic CRC have changed the criteria for resection. In the past, surgical candidates were those with no more than 3 tumors, tumors less than 5 cm in greatest diameter, no bilobar disease, no extrahepatic disease, and tumors that could be removed with at least a 1-cm margin of normal hepatic parenchyma. In the modern era of hepatic surgery, the number of candidates for resection has been raised by innovative techniques to increase residual hepatic reserve (portal vein embolization, 2-stage hepatectomy, and radiofrequency ablation) and by neoadjuvant administration of systemic agents to shrink hepatic tumors. Oxaliplatin-based regimens can convert up to 20% of nonoperative cases into operative cases;\(^5\) the 33% 5-year survival rate for these patients is similar to that for many patients who undergo surgery without prior chemotherapy.\(^5\)\(^-\)\(^6\)

Neoadjuvant therapy has also been effective for patients with extrahepatic disease, which previously was considered an absolute contraindication to surgery.

In this article, Oussoultzoglou and colleagues report a large prospective single-institution study that evaluated the prognostic role of CEA in patients undergoing resection of hepatic metastases from CRC. Despite the inclusion of patients with multiple tumors and extrahepatic disease, the median survival was 32.2 months. A reduction in CEA level 6 weeks after surgery correlated with prolonged survival. These findings suggest that CEA is a good prognostic indicator and might improve the selection of patients for adjuvant chemotherapy.

However, the bigger challenge is to identify patients likely to benefit from resection without prior neoadjuvant chemotherapy. First-line resection eliminates the risk of hepatic progression during neoadjuvant therapy, as well as the operative and postoperative problems associated with the hepatotoxic effects of chemotherapy (steatosis, steatohepatitis, and sinusoidal obstruction).\(^7\) Operative morbidity is directly related to the duration of preoperative chemotherapy. Karoui et al\(^8\) reported that the complication rate was 54% after 6 or more cycles of chemotherapy compared with 19% after fewer than 6 cycles. Moreover, although the rate of complete radiographic response to systemic biochemotherapeutic regimens can reach 20%, the pathologic response may be incomplete.\(^9\) These patients may require “blind hepatectomy” at the tumor site, which is far less preferable than first-line resection based on radiographically visible tumors.

An argument in favor of neoadjuvant therapy is that reduced tumor burden can increase the likelihood of complete resection with negative margins. In addition, neoadjuvant treatment can be used to evaluate biologic response. Finally, neoadjuvant treatment may improve the...