ORIGINAL ARTICLE

Effectiveness of Positron Emission Tomography for Predicting Chemotherapy Response in Colorectal Cancer Liver Metastases

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Hypothesis: Chemotherapeutic agents may be able to convert unresectable colorectal hepatic metastasis to resectable disease, therefore changing the surgical options. The role of positron emission tomography (PET) for patients undergoing chemotherapy remains unclear. We hypothesize that recent chemotherapy treatment could result in false-negative PET results.

Design: Case-control study evaluating PET findings.

Setting: The University of Texas M. D. Anderson Cancer Center.

Patients: From May 1, 2006, through August 31, 2008, data for 224 consecutive patients were entered into a prospective database for evaluation of hepatic metastasis of colorectal carcinoma. One hundred thirty-eight patients underwent PET and conventional imaging (a combination of computed tomography, magnetic resonance imaging, and ultrasonography). All had oncologically sound colorectal operations.

Interventions: Liver resection or ablation for colorectal liver metastases.

Main Outcome Measures: To determine the accuracy of PET scans to detect residual viable colorectal cancer liver metastases after a significant response to systemic chemotherapy.

Results: Patients with biopsy-proven disease underwent hepatic resection (120 patients [87.0%]), radiofrequency ablation (2 [1.4%]), or resection with radiofrequency ablation (7 [5.1%]). Nine patients (6.5%) had inoperable disease that was found intraoperatively. When performed within 4 weeks of chemotherapy, PET had a negative predictive value of 13.3% and a positive predictive value of 94.3%. The sensitivity was 89.9%, the specificity was 22.2%, and the accuracy was 85.5%.

Conclusions: Positron emission tomography within 4 weeks of chemotherapy is not a useful test for evaluation of colorectal hepatic metastases. The high rate of false-negative results is likely due to metabolic inhibition caused by chemotherapeutic drugs. We recommend that physicians not use PET in patients recently completing chemotherapy; they should undergo the appropriate oncologic hepatic operation based on the high probability of viable malignant disease.

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THE ROLE OF SURGERY IN colorectal hepatic metastases is undergoing a revolution of sorts. For example, a few years ago an extrahepatic metastasis effectively eliminated surgical resection, but a combination of chemotherapeutic options and surgical techniques has expanded the indications for resection and increased the population of patients who may benefit.[1,2] Neoadjuvant chemotherapy has increased the resectability rate by 11% to 37%.[1] Unfortunately, greater than 80% of patients undergoing hepatic resection will have recurrences, mostly within the first 2 years.[2] Nonetheless, the only hope for cure is resection, and prior surgical dogma based on the number of lesions, size of the tumor-free resection margin, and presence of resectable extrahepatic disease must be questioned.[3-5] The current standard approach to surgical planning is contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) for specific tumor characteristics or contraindications to CT.[6] Several series showed that focal extrahepatic

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disease, an isolated pulmonary lesion, can be safely resected, with 5-year survival rates of 29% to 58%.[7,8] In 1 series,[7] 17 of 30 patients required 3 or more resections. Clearly, this is an extremely selected patient population.

As the opportunities to resect hepatic and focal extrahepatic colorectal metastases continue to improve, choosing the appropriate patient population becomes imperative. Imaging modalities such as CT and MRI provide detailed anatomic information regarding the nature of the lesion but no functional information. Transcutaneous ultrasonography is even less invasive but often less accurate.[9] Finally, positron emission tomography (PET) using fluorine-18–labeled deoxyglucose detects increased metabolic activity (uptake). This can represent metastatic disease, new primary disease, infectious causes, inflammation, or any increase in the cellular use of glucose.

At present, the poor anatomic resolution of PET does not allow for its isolated use to plan operations; however, it is often used in combination with CT and/or MRI for diagnostic imaging.[1,6,9] Exactly what PET adds to surgical decision making remains unclear. A meta-analysis[9] found that PET had higher sensitivity rates (76%) for detection of malignant lesions than did helical CT (64%) or MRI (71%). That meta-analysis included 61 articles from 1990 to 2003. The criterion standard applied was pathologic tissue diagnosis. Chemotherapy changes the activity of a malignant lesion,[1,10,11] but exactly how much is unclear. There appears to be a correlation between decreasing PET uptake and reduction in tumor burden; however, hypometabolic lesions may still harbor viable malignant cells.[10,11] In addition, the authors reviewed the temporal relationship between chemotherapy and false-negative and false-positive results on PET. The false response rate has been reported to be up to 20% if PET is performed within 5 weeks of chemotherapy treatment.[10] Thus far, similar studies[11] have had too few patients to reach a conclusive decision regarding the role of PET in colorectal hepatic metastases.

Therefore, we reviewed our patient population for the temporal relationship between PET results and tissue-proven hepatic metastases from colorectal carcinoma. The impetus for this research was finding viable cancer in patients with clearly negative findings on PET. We hypothesized that PET uptake levels were artificially decreased after chemotherapy. That is, lesions that appeared to be nonmalignant were actually viable malignant lesions.

METHODS

From May 1, 2006, through August 31, 2008, data for 224 consecutive patients were entered into a database for evaluation of hepatic metastasis of colorectal carcinoma. All underwent oncologically sound colon resections. One hundred thirty-eight patients underwent PET and conventional imaging (a combination of CT, MRI, and ultrasonography). The presumptive diagnosis was hepatic metastatic disease. No patient had only PET results, and all PET was performed in the latter half of the chemotherapeutic protocol or within 4 weeks of terminating chemotherapy. All patients had tissue-proven diagnoses of hepatic metastases.

Patients underwent exploratory laparotomy to exclude the presence of unresectable extrahepatic metastatic disease. Intraoperative ultrasonography was used in all cases to detect the location and size of hepatic tumors and to guide the decision to proceed with an anatomic (hemihepatectomy or segmental resection) or nonanatomic (wedge) resection. Only 9 patients (6.5%) received radiofrequency ablation as the therapeutic component of their liver procedure after biopsy findings consistent with metastatic disease. Where available, we reviewed which chemotherapeutic regimen patients received before or during PET.

We used SPSS statistical software (version 11.04; SPSS Inc, Chicago, Illinois) to analyze the data. Statistical significance was set at $\alpha = .05$. The institutional review board of our hospital approved this study.

RESULTS

Two hundred twenty-four patients met the initial criteria. However, only 138 had at least 1 PET scan subsequent to chemotherapy and before liver intervention. The average age was 56 years; the population included 86 men (62.3%) and 52 women (37.7%). Hepatic metastases were initially diagnosed using PET in 39 patients (28.3%). Nineteen of these 39 (49%) underwent resection without additional imaging; typically, they had a recent CT scan that provided sufficient anatomic detail to proceed with a resection. One patient had a metastatic lesion with a negative finding on CT and a positive finding on PET. No patient had PET-positive and MRI-negative findings. In addition, no further site of disease was seen on PET that was not previously seen on CT, MRI, or ultrasonography or during intraoperative assessment.

The primary diagnosis was mucinous colonic carcinoma in 2 patients and adenocarcinoma in 136 patients. At initial presentation for the primary colorectal lesion, 70 (50.7%) had metastatic disease. Before resection of the primary tumor, 97 (70.3%) had no neoadjuvant therapy. Twenty-two (15.9%) had chemoradiotherapy, whereas 19 (13.8%) received only chemotherapy as their neoadjuvant therapy. Most patients underwent multimodality imaging of their thorax and abdomen after their colorectal surgery; 3.2% were diagnosed as having liver metastases at the time of their primary colorectal procedure, 4.0% with ultrasonography, 9.5% with MRI, 52.4% with CT, and 31.0% with PET, as seen in the following tabulation listing the initial methods of diagnosis.

Method	No. (%) of Patients[a]
Primary operation	4 (3.2)
MRI	12 (9.5)
CT	66 (52.4)
PET	39 (31.0)
Ultrasonography	5 (4.0)

[a] Twelve patients (8.7%) presented to our institution with multiple studies or incomplete records showing liver metastases, and a single primary source of diagnosis could not be determined, leaving 126 patients available for this analysis. Because of rounding, percentages may not total 100.

Patients with biopsy-proven disease underwent hepatic resection (120 patients [87.0%], radiofrequency ablation [1.4%], or resection with radiofrequency ablation [5.1%]. After chemotherapy delivered for 4 weeks or less in advance of liver resection (**Table 1**), the false-negative rate for hepatic metastasis of the PET was 86.7% (n=13) with a negative predictive value (NPV)

Table 1. Chemotherapy Before Positron Emission Tomography[a]

	No. (%) of Patients
FOLFOX plus bevacizumab	76 (60.3)
FOLFOX	24 (19.0)
FOLFOX plus cetuximab	5 (4.0)
Oxaliplatin, bevacizumab, and capecitabine	5 (4.0)
Fluorouracil	3 (2.4)
Other	13 (10.3)
Capecitabine	2 (1.6)
FOLFIRI plus bevacizumab	2 (1.6)
FOLFOX plus panitumumab	2 (1.6)
Fluorouracil and irinotecan hydrochloride	1 (0.8)
Capecitabine, irinotecan, and bevacizumab	1 (0.8)
FOLFIRI	1 (0.8)
FOLFOX plus bevacizumab and cetuximab	1 (0.8)
FOLFOX plus irinotecan	1 (0.8)
Irinotecan, cetuximab, and bevacizumab	1 (0.8)
Oxaliplatin, bevacizumab, and irinotecan	1 (0.8)

Abbreviations: FOLFIRI, leucovorin (folinic acid), fluorouracil, and oxaliplatin; FOLFOX, leucovorin calcium (folinic acid), fluorouracil, and oxaliplatin.

[a] Includes patients receiving chemotherapy for colorectal carcinoma after colon resection with subsequent diagnosis of hepatic metastases (n=126); 12 patients (8.7%) were missing.

Table 2. Relationship Between Positron Emission Tomography (PET) Results and Hepatic Lesions[a]

	Hepatic Metastases, No. of Patients	
PET Results	Positive	Negative
Positive	116	7
Negative	13	2

[a] Includes tissue-proven results of PET after chemotherapy. Readings were by experienced radiologists with expertise in abdominal cancer.

of 13.3% (2 true-negative and 13 false-negative findings). These patients underwent hepatic wedge resection and possible ablation based on CT or MRI findings despite negative PET findings. The odds ratio for predicting hepatic metastasis vs a benign cause was 2.55 (95% confidence interval [CI], 0.55-12.21 [*P*=.25]). As a test, PET yielded 116 true-positive, 13 false-negative, 7 false-positive, and 2 true-negative findings (**Table 2**). The sensitivity rate for PET was 89.9%, with a specificity rate of 22.2%. The positive predictive value (PPV) was 94.3% (116 true-positive and 7 false-positive findings). The accuracy was 85.5%, as seen in the following tabulation.

Statistical Measure	Percentage (95% CI)
Sensitivity	89.9 (83.3-94.5)
Specificity	22.2 (2.8-60.0)
PPV	94.3 (88.6-97.7)
NPV	13.3 (1.7-40.5)
Accuracy	85.5 (78.5-90.9)

Nine of 10 patients (90%) with poorly differentiated colon adenocarcinoma metastases had positive PET findings.

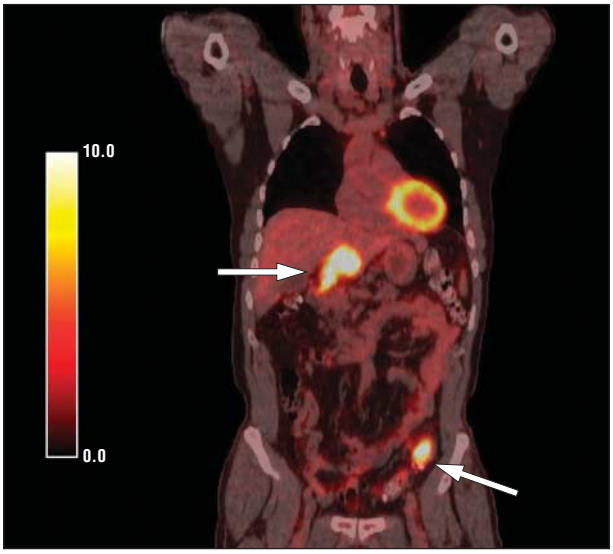

Figure 1. Hypermetabolic regions of the primary tumor (distal sigmoid colorectal adenocarcinoma) and biopsy-proven hepatic metastatic disease are denoted by arrows. Background (normal) metabolism is seen in other parts of the gastrointestinal tract. The patient is a man aged 61 years. The scale is given in standard uptake values.

More than 85% of patients had a reduction of greater than 25% in hepatic tumor burden after chemotherapy according to multimodality imaging results. Slightly less than half of the patients had a reduction of greater than 50% in their metastasis, as seen in the following tabulation.

Pathologically Confirmed Radiologic Response	No. (%) of Patients[a]
Complete (>90%)	3 (3.4)
Major (>50% to 90%)	35 (40.2)
Minor (25% to 50%)	37 (42.5)
None (<25%)	12 (13.8)

[a] Results are included only if comparisons are with actual previous imaging studies (n=87). Previous studies were missing in 51 patients (37.0%). Because of rounding, percentages may not total 100.

Of this very select group of patients, we report a 93.5% survival rate at a median follow-up time of 15 months (range, 1 week to 6 years). Median time to death after the first 90 days (n=7) was 9.4 (range, 6.5-48.3) months. There was a single perioperative death (at 1 week) and another death during the first 90 days for a total 90-day mortality rate of 1.4%.

COMMENT

The management of metastatic colorectal carcinoma is evolving drastically. Often, PET is used as confirmation of CT/MRI findings or for whole-body surveillance. Within 4 weeks of chemotherapy, however, liver lesions may or may not be adequately identified on CT/MRI, and these are not reliably identified on PET (**Figure 1** and **Figure 2**). Figure 1 clearly shows a primary colorectal adenocarcinoma and liver metastasis in a man aged 61 years. This CT-PET reconstruction demonstrates the possible value of PET. Unfortunately, as we report, this correlation or confirmation between CT and PET is not uniform. The patient in Figure 2 underwent

an oncologically sound partial colectomy with hepatic recurrence 6 months after surgery. The PET portion of the scan clearly yielded negative findings. However, this patient had pathologically proven metastatic disease. This is seen on the CT portion of the image (changes in the gray scale rather than the intensity of red pseudocolor) of Figure 2.

As we described, the sensitivity rate for PET in this setting is relatively high at 89.9%, suggesting that the ratio of true-positive to false-negative values is high. This is true, but it is incomplete. Comparing false-negative with true-negative findings (the false-negative rate) yields a slightly different picture: an 86.7% false-negative rate (equivalent to stating a 13.3% NPV). That is, when the PET finding is negative, it cannot be trusted (Figure 2). The NPV depends on the population being analyzed, which is where this unique situation develops.

The prevalence of early hepatic metastatic disease is high (the median disease-free interval is <1 year after colon resection),[6] whereas PET findings will be positive only for metabolic activity above baseline. The goal of chemotherapy is to decrease malignant cell metabolic activity, ideally, to zero and induce apoptosis/necrosis and cell death. A priori, then, PET would not be expected to yield useful information after an effective chemotherapeutic regimen until malignant cells recovered enough metabolic activity that is greater than the surrounding tissues. Our results confirm this finding, and they are in line with other evidence in the literature.[9,10] Exactly how long to wait after chemotherapy until PET becomes useful is unknown, but longer than 8 weeks seems reasonable.

Most of these patients undergo abdominal-pelvic CT before initial colon resection, and comparing that scan with postchemotherapeutic imaging may be a better alternative. Changes in lesions (or any new lesions) are then treated accordingly. If a lesion is worrisome on CT or MRI within 4 to 6 weeks of finishing chemotherapy, it should then be surgically removed regardless of the PET results. In this study, the PPV was very high (94.3%). Again, the PPV varies with the population being studied, as described in other studies.[1,6,9] The prevalence of hepatic metastases is greater than 50% during the first 5 years after diagnosis. On surveillance imaging, a positive PET finding without CT findings poses a diagnostic dilemma if the temporal relationship to chemotherapy is short. Of the 7 false-positive findings, PET was the modality of diagnosis in 3 (43%). This suggests that 3 of the 138 operations (2.2%) would have been prevented if PET had not been performed. This rate is similar to those of other cost-benefit and decision analyses.[12] Another report[13] suggests that up to 24% of patients with negative preoperative imaging results show macroscopic disease at the time of operation at that same site.

Furthermore, there were only 10 patients with poorly differentiated colon adenocarcinoma liver metastases. One of these 10 had a negative PET finding. The PPV of 94.3% and the small proportion of poorly differentiated lesions (10 of 138 [7.2%]) suggest that these results are valid for nearly all patients regardless of the degree of differentiation of their disease.

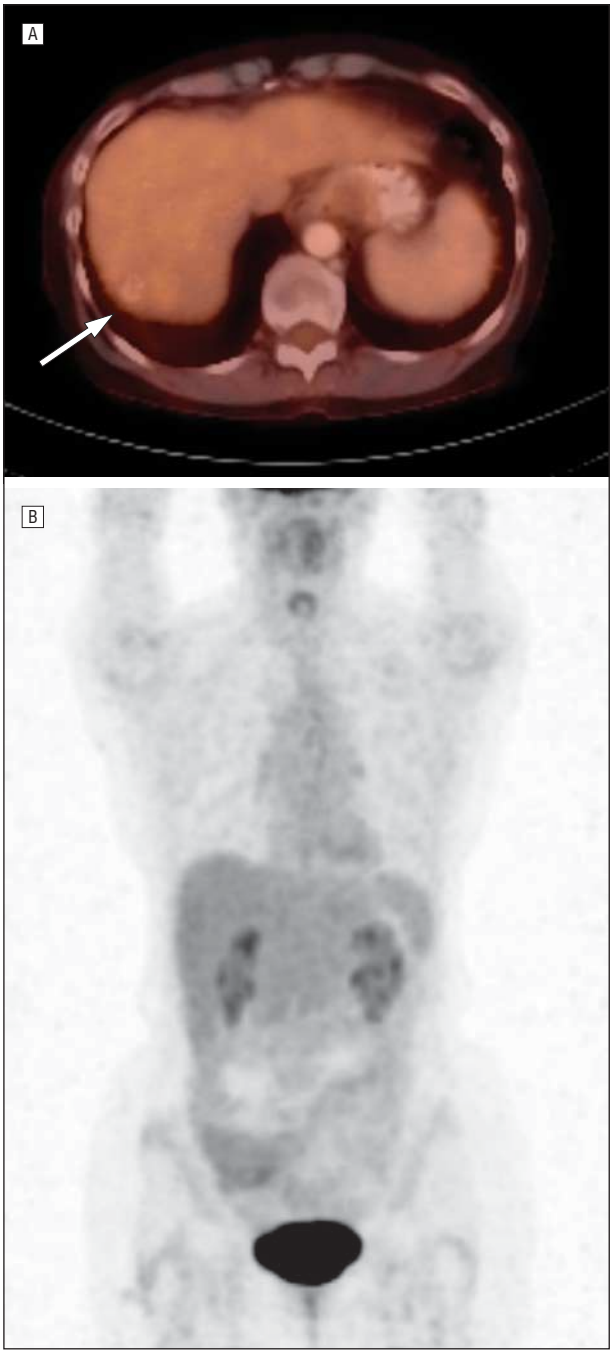

Figure 2. Detection of a metastatic liver lesion 6 months after resection of a colorectal carcinoma. A, A biopsy-proven metastatic liver lesion is seen on the computed tomography (CT) component of the CT–positron emission tomography (PET) study (arrow). B, The lesion is not seen on either the PET or the CT portion of a combined CT-PET study.

No survival benefit has been seen in the use of PET by other groups.[6,12] We had a median follow-up of 15 months with 93.5% of patients alive. This population is obviously extremely selected but shows that, in a selected population, clinically significant improvements can be made. Of those dying despite surgery, the median time to death was 9.4 months. The Surveillance, Epidemiology, and End Results data[14] show an 11% 5-year survival rate with distant disease. It is difficult to extrapolate how many of our patients will be alive at 5 years, but

it appears that this population benefits from surgical intervention for their metastatic disease.

Finally, the distinction between radiologic and pathologic responses is an important one. The current technological age allows for unprecedented imaging before surgical intervention. This, coupled with the increasing evidence-based approaches to surgery, not only allows but requires that we investigate surgical decision making. Investigators at our own institution[15] recently showed that pathologic response is an independent predictor of survival in these patients. Although imaging techniques are very valuable, functional studies are not sufficiently accurate for surgical planning or decision making. An interesting study would begin serial PET scans at the time of initial primary colorectal cancer diagnosis at colonoscopy. Although this would be expensive, it would quantify the effects of multiple therapies, the patient's global health, and chemotherapeutics on the functional status of these lesions. At present, few of our patients undergo PET before receiving any treatment; therefore, the likelihood of a negative finding a priori is not known for this population. However, if these findings were all positive, we would still not recommend performing repeated PET after chemotherapy. In addition, if these previously positive findings on PET were negative after chemotherapy, this would provide further support to not perform follow-up PET.

At current practice, our algorithm is as follows: If chemotherapy has not been given for 6 weeks or longer, we recommend patients undergo CT-PET with reconstructions. If chemotherapy is ongoing or has been administered within the past 6 weeks, we recommend CT or MRI only, obtaining whichever type of scan that the patient has undergone previously to allow direct comparison. Prior comparisons are one of the most important tools in determining the likelihood of a malignant lesion and response to therapy. If there are any suspected malignant lesions or changes, we recommend resection if possible, ablation if not.

CONCLUSIONS

A unique situation arises in the use of PET with hepatic metastases of colorectal carcinoma during or soon after chemotherapy. Routine surveillance with CT or MRI often yields findings for metastatic disease, but clinical confirmation is desired. Unfortunately, although the accuracy rate is 85.5%, this test should not be used in surgical decision making. A positive test result does not alter the surgical plan, whereas a negative test result should not be trusted. This is a slightly unusual high-prevalence metastatic disease with a reasonably good test (PET). Owing to the nature of the metastatic disease and the poor prognosis, aggressive surgical intervention is warranted. Positron emission tomography allows for confirmation, but it does not and perhaps should not change the surgical recommendations to the patients and their families within 4 to 6 weeks of receiving chemotherapy because the NPV is too low. A randomized, controlled trial would clearly answer the questions, but the ethics involved in not subjecting worrisome lesions to biopsy after nonfunctional studies (ie, CT or MRI) are prohibitive. More aggressive percutaneous biopsy might be an appropriate compromise in a highly selective situation, but even in the presence of isolated extrahepatic disease, definitive surgical intervention yields the best chance for survival.

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INVITED CRITIQUE

Positron Emission Tomography for Colorectal Cancer Liver Metastases

Where's the Value?

Advances in chemotherapy during the past decade have created an evolving paradigm for treating patients with liver metastases from colorectal cancer, particularly in increasing the resectability rate.[1] The management of disease in these patients relies heavily on imaging with CT and MRI. Positron emission tomography is frequently used. In the preceding article, Glazer et al retrospectively analyzed the utility of PET in the management of disease in these patients. This article is important because it highlights the limitations of PET in predicting response to chemotherapy. Figures 1 and 2 nicely demonstrate the problem. Despite a negative PET finding, viable tumor is likely to be present. The NPV of PET performed within 4 weeks of chemotherapy was 13.3%.

As the authors postulate, chemotherapy interrupts the metabolism of tumor cells to induce apoptosis and cell death. Some cells may survive with metabolic activity similar to that of the surrounding tissue and thus cannot be detected on PET 4 weeks after chemotherapy. The optimal timing for performing PET after chemotherapy is not known, but it is likely that there will be fewer false-negative scans after a longer interval following completion of chemotherapy.

In this study, only a few patients had PET before any therapy, so the metabolic activity of the primary tumor and its ability to be visualized on PET is unknown. Also, although the PPV of PET was 94.3% in this study, a positive finding did not change the surgical plans.

Positron emission tomography is expensive and should be used only if the results will alter management.

I agree with the authors that surgical decisions should not be based on the results of PET without further investigation. The algorithm that they offer is reasonable and relies on a comparison of current with prior CT or MRI findings. The movie is usually more useful than the snapshot, in particular to identify change. Despite the authors' findings in this study, their algorithm recommends PET be performed if more than 6 weeks have lapsed since chemotherapy. Why should we trust a negative PET finding 6 weeks after chemotherapy? I would hope that the authors and others will continue to evaluate this in well-managed trials. Until that time, surgical decisions in patients with colorectal liver metastases should be based on careful clinical evaluation and serial CT or MRI studies.

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