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Abbreviation:
CEA = carcinoembryonic antigen

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Hepatic Metastases from Colorectal Cancer: Preoperative Detection and Assessment of Resectability with Helical CT[1]

PURPOSE: To prospectively evaluate helical computed tomography (CT) in the preoperative detection of hepatic metastases and assessment of resectability with surgical, intraoperative ultrasonographic (US), and histopathologic correlation.

MATERIALS AND METHODS: Between October 1995 and December 1998, preoperative staging with helical CT (5-mm collimation; reconstruction interval, 5 mm) was performed in 157 patients with hepatic metastases. Iodinated contrast material was injected intravenously (160–170 mL; rate, 2.5–3.0 mL/sec); acquisition began at 60–70 seconds. Four radiologists prospectively assessed the metastatic involvement of the liver by indicating the number and location of the lesions; resection was indicated in 113 patients (119 instances). Helical CT findings were correlated with pathologic and surgical findings on a lesion-by-lesion basis.

RESULTS: Intraoperative US, palpation, and histopathologic examination revealed 290 liver metastases; helical CT correctly depicted 247. Helical CT results were the following: overall detection rate, 85.1% (95% CI: 80.8%, 89.3%); positive predictive value, 96.1% (95% CI: 92.9%, 98.1%); and false-positive rate, 3.9% (10 of 257 findings; 95% CI: 1.9%, 7.1%). False-positive findings were related to hemangioendothelioma, hemangioma, hepatic peliosis, biliary adenoma, centrilobar hemorrhage, biliary hamartoma, periportal fibrosis, and normal liver parenchyma. Curative resection was performed in 112 instances with a resectability rate of 94.1%. Four-year patient survival rate was 58.6%.

CONCLUSION: Helical CT is a noninvasive, reliable, and accurate technique for imaging the liver and should be considered as the standard preoperative work-up of hepatic metastases from colorectal cancer.

It is estimated that colorectal cancer is the second most frequent cause of cancer mortality in the United States, with approximately 55,000 deaths in 1996 (1). The liver is a common site for metastasis in patients with colorectal carcinoma (2,3). In a substantial proportion of patients who die of metastatic disease, metastases are exclusively in the liver (3,4). Although the prognosis of nontreated hepatic metastases is dismal, some patients with limited hepatic disease can benefit from resection. Experience in recent years has shown that hepatic surgery for colorectal cancer metastasis provides an effective therapeutic approach in a substantial proportion of patients. Investigators in recent surgical series (5–7) report 5-year survival rates of up to 20%–40%. Consequently, as perioperative mortality and morbidity rates have become acceptable, hepatic resection is the only curative option for the treatment of isolated hepatic metastasis today.

Previous investigators (3) have emphasized that only a small proportion of patients with colorectal metastases are candidates for resection with curative intent. Tumor recurrence has been reported (5,7,8) in up to 60% of the patients undergoing resection. Therefore, accurate preoperative staging is mandatory in potential candidates for curative surgery.

A number of imaging modalities, including computed tomography (CT), CT during arterial portography, gadolinium-enhanced magnetic resonance (MR) imaging, and ferumoxides-enhanced MR imaging (9–14), are available for preoperative staging of liver disease. The purpose of our study was to prospectively assess the sensitivity and specificity of helical CT in the detection of hepatic metastasis from colorectal carcinoma in a homogeneous series of patients from a single institution, with surgical, intraoperative ultrasonographic (US), and histopathologic findings as the standard.

MATERIALS AND METHODS

Patients

Between October 1995 and December 1998, 157 consecutive patients suspected of having hepatic metastases were referred to our hospitals for preoperative assessment. Patients were included in the study if they had colorectal carcinoma and (*a*) were suspected of having hepatic metastases at US or conventional nonhelical CT or (*b*) had increased levels of carcinoembryonic antigen (CEA). Because our institution is a referral center for hepatic surgery, most patients were referred from other hospitals. Techniques used in diagnostic procedures performed at outside institutions varied widely, and the findings were not always available for review. Thus, helical CT was performed in all instances at our hospital as a preoperative staging procedure to determine if the patients were candidates for hepatic resection. Our study was approved by our institutional review board, and informed consent was obtained from all patients.

Forty-four patients were excluded because they were considered unsuitable on the basis of preoperative imaging findings and did not undergo surgical exploration.

Our final study group comprised 113 patients who underwent surgical exploration in 119 instances; 106 patients underwent partial hepatectomy, six patients underwent repeat hepatectomy, and seven patients with nonresectable disease underwent surgical exploration and intraoperative US. There were 71 men and 42 women with a mean age of 58.9 years (age range, 33–77 years). The primary tumor originated in the rectum in 45 (39.8%) of the 113 patients and in the colon in 68 (60.1%) patients. Hepatic metastases were synchronous with the initial diagnosis of colon cancer in 34 instances and metachronous in 85 instances. Seventy-two (85%) of the 85 metachronous hepatic metastases were discovered during the first 3 years after resection of the primary colorectal cancer. In three patients, histopathologic results after surgical resection showed only benign hepatic lesion without evidence of metastasis.

The interval between surgical resection of the primary tumor and detection of hepatic metastases ranged from 2 to 61 months (mean, 19.2 months). The CEA level was preoperatively determined in 107 patients, with values ranging from 0.1–585.0 μg/L (mean, 38.8 μg/L). Increased levels (>5.0 μg/L) of CEA were detected in 66 (62%) of the 107 patients.

Helical CT Technique

Preoperative staging was performed in all patients at helical CT. A total of 119 sets of preoperative helical CT scans were prospectively evaluated. In all patients, the abdominal study was performed after intravenous administration of contrast material. Helical CT was performed with a ProSpeed Plus system (GE Medical Systems, Yokogawa, Japan). Scans of the liver were acquired with 5-mm collimation and a pitch of 1:1.5 and were subsequently reconstructed at 5-mm intervals. We used 300 mA and 120 kV. Ionic (Urografin 370 [meglumine diatrizate]; Schering, Berlin, Germany; 370 mg of iodine per milliliter) or nonionic (Ultravist 300 [iopromide], Schering or ioversol, Mallinckrodt Medical, Montreal, Canada; 320 mg of iodine per milliliter) contrast material was injected at a rate of 2.5 (160 mL, $n = 26$) or 3.0 mL/sec (170 mL, $n = 93$) by using a MCT power injector (MedRad, Pittsburgh, Pa). The helical breathhold acquisition began at 60–70 seconds. In patients who were suspected of having hemangiomas during portal phase imaging, delayed scans were also obtained. The rest of the abdomen and pelvis was studied in the cluster mode with 5-mm collimation and 10-mm intervals. If the attending radiologist considered the findings in the pelvis or retroperitoneum to be questionable, additional images of 5-mm sections with 5-mm intervals were obtained in the area of interest.

Surgical Procedures

Surgical exploration with the intention of curative hepatic resection was performed in 119 instances. Curative resection was defined as any resection in which the surgeon considered that all hepatic lesions were removed with a minimum margin of 1 cm.

Image Interpretation and Analysis

Before patients underwent surgery, at least two of four experienced radiologists (C.V., A.G., E.A., A.S.) prospectively assessed the metastatic involvement of the liver in a consensus reading. In all instances, the radiologists knew that the patient had colorectal carcinoma and was suspected of having hepatic metastases, but they were unaware of the results of the other diagnostic procedures. For radiologic-histopathologic correlation, the number, size, and location according to the Couinaud numbering system of focal lesions were noted.

At helical CT, metastatic lesions were defined as nodular low-attenuating lesions without characteristic findings of benign lesions (cysts or hemangiomas). Cysts were defined as water-attenuating lesions with no visible wall and no contrast enhancement. Hemangiomas were defined as low-attenuating lesions with discontinuous globular peripheral contrast enhancement and attenuation that was the same as that of the aorta. Indeterminate lesions were considered metastatic. The imaging findings were recorded in an electronic database.

All surgical resections were performed or were closely supervised by one surgeon (J.F.). The extent of hepatic disease was assessed by means of bimanual palpation and intraoperative US. Hepatic surgeons performed intraoperative US by using a flexible system (SSD-1100; Aloka, Tokyo, Japan) and a 5.0- or 7.5-MHz intraoperative probe to confirm the number and size of the metastases, as well as the relationship with vascular landmarks. In addition, benign lesions depicted at helical CT were confirmed at intraoperative US, and nonresected hepatic segments were thoroughly evaluated for occult hepatic metastasis.

Histopathologic specimens were carefully sliced, and direct radiologic-histopathologic correlation was obtained. The pathologist (T.S.), the surgeon, and one radiologist performed the radiologic-histopathologic comparison. Each detected lesion was measured and examined microscopically. The results of radiologic-histopathologic correlation and of surgical palpation and intraoperative US in nonresected portions of the liver constituted the standard of reference for our study.

The findings at histopathologic and surgical examination were compared with helical CT results and were stored in

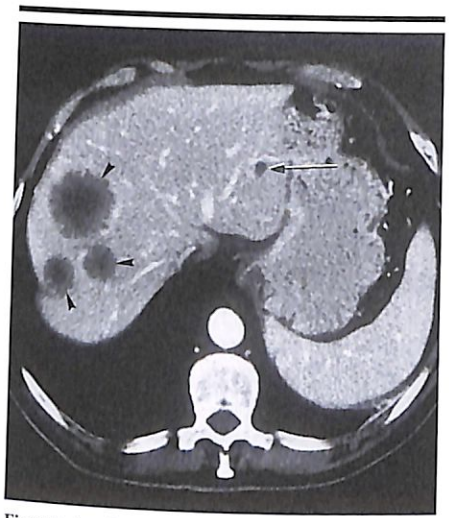
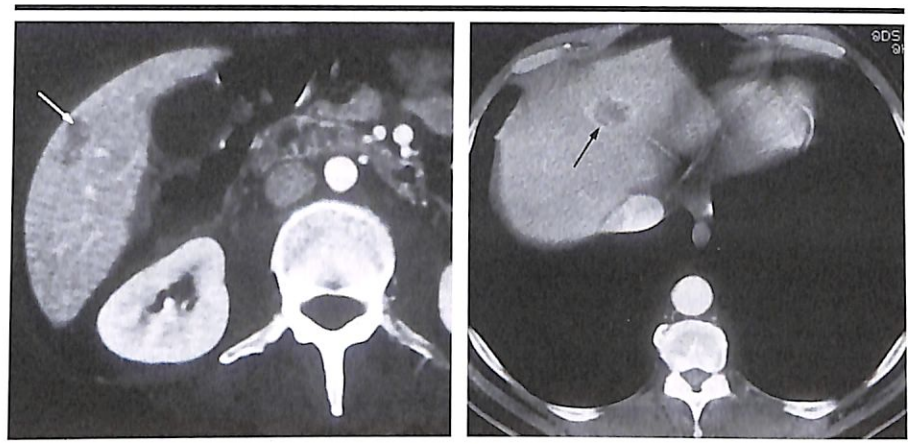


Figure 1. Transverse helical CT image obtained in a 57-year-old man with hepatic metastases from colorectal cancer shows a small cyst (arrow) in segment II and three low-attenuating lesions (arrowheads) that have peripheral contrast enhancement consistent with metastasis in segment VIII. Radiologic findings were confirmed at surgery, and segment VIII was resected.



a. b.

Figure 2. Transverse helical CT image shows false-positive findings. (a) Image obtained in a 46-year-old woman with colorectal cancer shows hepatic metastases in the upper segments of the right lobe (not shown) and a low-attenuating lesion (arrow) in segment V that was prospectively considered to be metastatic. At histopathologic examination, the lesion was a hemangioma. (b) Image obtained in a 55-year-old-man with colorectal cancer shows a low-attenuating lesion (arrow) in segment IV with peripheral rimlike contrast enhancement. The lesion was considered to be a metastasis and was resected. Histologic examination revealed that it was a hemangioendothelioma.

the database. Hepatic lesions that were recorded as metastases in the database and that had the same location and a similar size at CT and at surgery or histopathologic study were considered to be true-positive. Metastatic lesions detected at histopathologic or surgical examination and missed at helical CT were considered to be false-negative. Hepatic lesions that were benign at surgical or histopathologic examination that were misclassified as metastases at helical CT were considered to be false-positive.

Sensitivity was defined as the number of metastases correctly depicted at helical CT divided by the number of metastatic lesions identified at histopathologic and surgical examination. The false-positive rate was defined as the number of false-positive lesions depicted at helical CT divided by the total number of lesions (true-positive plus false-positive). The false-negative rate was defined as the number of false-negative findings with helical CT divided by the total number of metastases at histopathologic examination. The positive predictive value was defined as the number of metastases correctly depicted at imaging divided by the total number of lesions considered to be metastatic at imaging. The 95% CIs were calculated for these values.

Follow-up and Clinical Outcome

Clinical or radiologic follow-up was performed in all patients. Follow-up was performed between 3 and 49 months (median, 18 months). After the first hepatic resection, all patients were followed up every 6 months and underwent liver function tests, serial determination of CEA levels, and helical CT with the same technique as that used in preoperative staging.

RESULTS

Lesion Detection: Radiologic-Histopathologic Correlation

Two hundred ninety metastatic lesions were depicted at intraoperative US, hepatic palpation, or histopathologic study. The size of metastases ranged from 0.4 to 12.0 cm (mean, 3.8 cm). Helical CT correctly depicted 247 metastatic lesions (Fig 1). The number of metastases in each patient ranged from 0 to 11 (mean, 2.4). The overall detection rate of metastatic lesions at helical CT was 85.1% (247 of 290; 95% CI: 80.8%, 89.3%), and the positive predictive value was 96% (95% CI: 92.9%, 98.1%). The false-positive rate was 3.9% (10 of 257 findings; 95% CI: 1.9%, 7.1%).

False-positive lesions.—Ten false-positive lesions were depicted in 10 patients (Fig 2). The false-positive findings were hemangioendothelioma (n = 1), hemangioma (n = 1), hepatic peliosis (n = 1), biliary adenoma (n = 1), centrilobar hemorrhage (n = 1), biliary hamartoma (n = 1), periportal fibrosis (n = 2), and normal liver parenchyma without definite lesion (n = 2).

In three of these patients with false-positive findings, no metastatic lesion was detected at surgery or histopathologic examination. Histologic results in these three patients were consistent with hemangioendothelioma, hepatic peliosis, and periportal fibrosis. In the remaining seven patients, seven lesions considered preoperatively as metastases were excised, and histopathologic findings demonstrated that they were benign lesions.

The overall false-positive rate in our series was 3.9% (10 of 257 findings). By considering only patients with false-positive findings and no metastatic hepatic disease, the false-positive rate was 1.2% (three of 257 findings).

False-negative lesions.—Helical CT depicted 41 false-negative lesions in 25 patients. The false-negative rate was 14.1% (41 of 290 lesions) on a lesion-by-lesion basis and 21% (25 of 119 patients) on a instance-by-instance basis. The size of these missed lesions ranged from 0.3 to 1.5 cm (mean, 0.7 cm).

In 20 patients, 36 metastatic lesions were not seen retrospectively, although the exact location of the metastasis was known. In four patients, four metastatic lesions were identified retrospectively as low-attenuating subcentimetric lesions, but a definite diagnosis of metastasis was not possible. In one patient, one 8-mm metastasis was clearly seen in segment III

as a homogeneously hyperenhancing lesion in the portal phase that was prospectively believed to be a hemangioma (Fig 3).

Benign hepatic lesions.—Helical CT correctly depicted 53 cysts in 27 patients, 13 hemangiomas in nine patients, and one focal nodular hyperplasia in one patient.

Results of intraoperative US.—Intraoperative US depicted two false-negative findings, one 1.5-cm lesion in segment VI and another 1.5-cm lesion in segment II. The overall sensitivity for intraoperative US was 99.3% (288 of 290 findings). Three false-positive lesions were depicted in three patients at intraoperative US; histopathologic study revealed granulomatous reaction in one patient and normal liver parenchyma without definite lesion in two patients. The positive predictive value for intraoperative US was 98.2%.

Resectability Rate

During these 4 years, 119 hepatic resections were attempted in 113 patients who were preoperatively examined with helical CT. Curative resection (partial hepatectomy or metastasectomy with adequate margins) was performed in 112 instances. Six of these patients had undergone previous hepatectomy for metastasis and repeat hepatectomy due to hepatic recurrence. In seven instances (five women, two men; mean age, 60 years; age range, 35–74 years), curative resection was unsuccessful, and only intraoperative US and bimanual surgical palpation were performed, with a resectability rate of 94.1% (112 of 119 instances) (Fig 4).

Factors associated with nonresectable metastatic lesions were peritoneal carcinomatosis ($n = 1$), lymph node metastases in the porta hepatis ($n = 1$), massive tumor infiltration of the diaphragm ($n = 1$), local spread of primary left-sided colon cancer to the left kidney ($n = 1$), missed metastasis located on the surface of the liver ($n = 2$), and erroneous localization of one metastatic lesion ($n = 1$). This last case occurred in a patient with multiple lesions in the right lobe in whom erroneous localization of one lesion (located in segment IV at preoperative CT and in segment II at intraoperative US) precluded right trisegmentectomy.

Follow-up and Clinical Outcome

By the end of the study, 45 (40.1%) of the 112 patients had tumor recurrence. Hepatic recurrence was detected in 21 (47%) patients, lung recurrence in 14 (31%), and local recurrence in seven (16%). Osseous and soft-tissue sites of recurrence were found in three patients. In 13 (29%) patients, more than one site of recurrence was detected. With a follow-up of 12, 24, 36, and 48 months (median, 18 months), survival was 89%, 74%, 58%, and 58%, respectively (Fig 5).

DISCUSSION

Preoperative imaging of hepatic metastases plays a critical role in patient selection and in planning the optimal surgical approach. A wide range of diagnostic techniques, including MR imaging, helical CT, and CT during arterial portography, is available for use in the preoperative assessment of hepatic metastasis. CT during arterial portography was formerly considered to be the single most sensitive imaging technique for use in the detection of hepatic metastases. However, due to the high false-positive rate (15) and the invasiveness of the procedure, serious doubts have been raised about its use. In addition, a number of recent reports have shown that helical CT and contrast material–enhanced MR imaging are highly accurate in the detection of hepatic tumors, with results that parallel or even surpass those of CT during arterial portography (9,11,12,16).

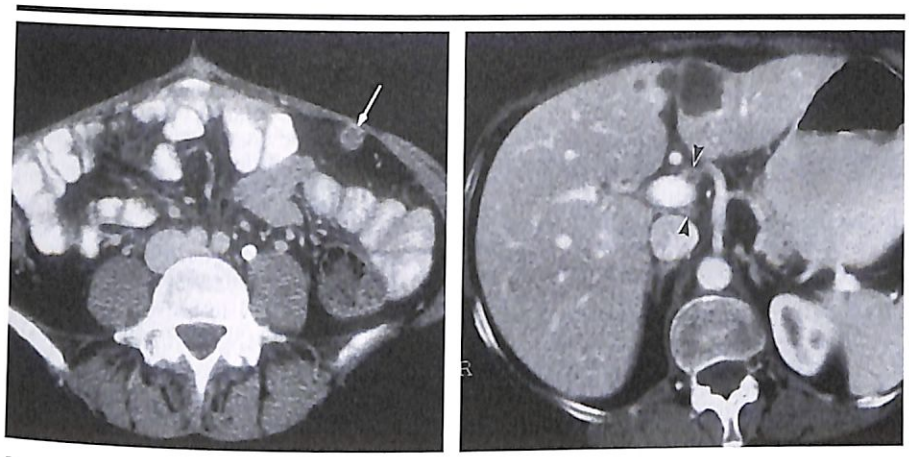
Previous results showed that ferumoxides-enhanced MR imaging (12) and helical CT (9) were at least as accurate as CT during arterial portography in the detection of hepatic metastases and that they depicted fewer false-positive lesions. These results suggest that adequate preoperative staging may be performed with noninvasive imaging techniques. However, despite recent improvements in noninvasive hepatic imaging technology, there is no general agreement in the literature concerning the imaging technique that should be routinely used in the preoperative evaluation of hepatic metastases.

Contrast-enhanced MR imaging with ferumoxides or gadolinium provides excellent results in the preoperative staging of hepatic metastases (10,16). However, MR imaging is more expensive than CT and is not as widely available. The goal of our study was to determine whether a noninvasive and widely available technique such as helical CT could be used as the only imaging technique in the preoperative staging of hepatic metastases from colorectal cancer.

In our study of a large number of patients from a single institution with careful radiologic-histopathologic correlation, we found that helical CT correctly depicted 247 (85.1%) of 290 hepatic metastases from colorectal cancer. False-positive lesions were found in 10 (3.9%) of the 257 instances, and the positive predictive value was high (96.1%). The sensitivity in our series is slightly better than that reported by Ward and co-workers (10) for malignant lesions with both biphasic helical CT (74%) and MR imaging after the administration of superparamagnetic iron oxide (81%). The improved results at helical CT in our series may be due to the higher dose of contrast material (170 vs 150 mL) and the thinner collimation used (5 vs 8–10 mm).

The use of the biphasic technique in the study of hepatic metastases as was performed in the series by Ward et al (10) is controversial. Arterial-phase imaging increases the detection of hypervascular tumors such as hepatocellular carcinoma or hypervascular metastases (17,18). However, most hepatic metastases from colorectal cancer are hypovascular and, therefore, are best imaged in the portal phase. Although there has been anecdotal evidence (19) in the literature that some hepatic metastases missed in the portal phase were visible in the arterial phase, some authorities (17,20) agree that an arterial phase is not necessary for

Figure 3. Transverse portal phase helical CT image obtained in a 77-year-old man with hepatic metastases from colorectal cancer shows false-negative findings. Image shows an enhancing lesion (arrow) with a small low-attenuating center in segment VI; this finding was consistent with metastasis and was confirmed at laparotomy. In the anterior portion of segment III, image shows a small homogeneously hyperenhancing lesion (arrowhead) that was prospectively considered to be a benign hemangioma. Histologic examination revealed that the lesion was a metastasis. Note the marked fatty infiltration of the liver that probably led to the misdiagnosis of the lesion.



a. b.

Figure 4. Transverse helical CT images show nonresectable lesions that were understaged. (a) Image obtained in a 45-year-old woman with colorectal cancer. Helical CT revealed two hepatic metastases (not shown) that were confirmed at surgery. However, the patient could not undergo resection because of peritoneal carcinomatosis that was not diagnosed prospectively. Retrospectively, a small peritoneal node (arrow) is depicted in the greater omentum and was the only sign of carcinomatosis at CT. (b) Image obtained in a 69-year-old woman with hepatic metastases shows the low-attenuating metastases, which were confirmed at surgery, in the left lobe. Note small (<1-cm) lymph nodes (arrowheads) in the porta hepatis. The lesions were deemed too small to be reliably considered metastatic, and the patient underwent surgery. At laparotomy, surgical biopsy of the lymph nodes revealed adenocarcinoma, and the patient did not undergo resection.

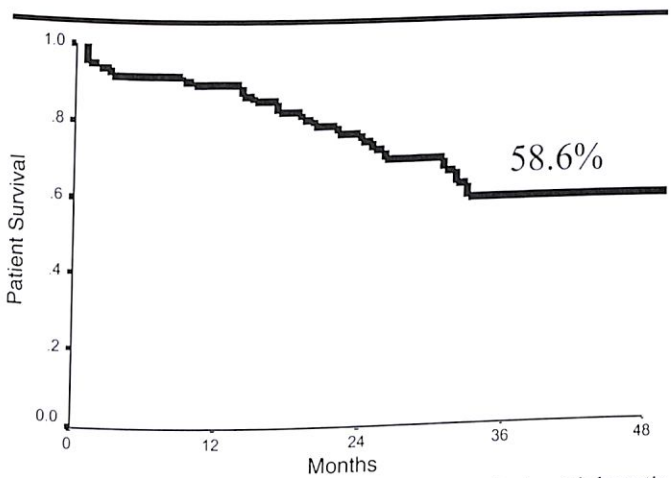


Figure 5. Graph shows overall survival rate in patients with hepatic metastases from colorectal cancer after potentially curative resection.

the study of metastases from colorectal cancer.

A strong radiologic-histopathologic correlation is critical for evaluating the results of a staging technique in hepatic metastasis. The problem is that imaging technology is changing quickly, and, in most cases, studies are flawed by the lack of strong histopathologic correlation (10,16) or by the fact that a state-of-the-art technique was not used. In our series, all patients underwent surgical exploration, and in 112 (94.1%) instances, patients underwent curative resection. In the series by Ward et al (10), 20 (39%) of the 51 patients did not undergo resection.

In a recent article by Semelka and coworkers (16), gadolinium-enhanced MR imaging was more sensitive than CT during arterial portography in the detection of hepatic metastases (96.8% vs 88.4%). However, in that study, only seven (35%) of 20 patients underwent curative resection. Interestingly, in our series, we had five discrepant findings at histopathologic study and intraoperative US (three false-positive and two false-negative findings) that were correctly diagnosed at helical CT.

Although intraoperative US is the most sensitive technique for the detection of hepatic lesions (21,22), in some instances the correlation of intraoperative US findings with histopathologic findings is not absolute. Thus, studies in which the results of intraoperative US alone are correlated with those of histologic examinations may be limited, and the metastatic involvement of the liver may be underestimated. Obviously, this flaw is inherent in every study in the literature in which the results of an imaging technique used in the detection of hepatic metastases of colorectal cancer are reported, since nonresected segments are studied only with intraoperative US. However, in our series, the histopathologic correlation was stronger than that of most reported series (10,11,16) because most patients underwent hepatic resection.

In addition, we prospectively assessed our ability to use helical CT to determine the resectability of the lesions. The issue of resectability has rarely been addressed in the radiology literature but is a widely discussed topic in the field of surgery. In the series of Rahusen et al (23), 54% of the patients with colorectal hepatic metastases that were apparently resectable at preoperative imaging (CT and US) were eventually not candidates for curative resection after diagnostic laparoscopy, laparoscopic US, and intraoperative US.

In the series of Jarnagin et al (24), 416 (77.9%) of the 534 patients who were considered to have resectable hepatic metastases could undergo resection. In this series, preoperative work-up was performed with different radiologic techniques (CT, CT during arterial portography, and MR imaging). In addition, no details of the technical parameters were reported; the authors stated that they used nonuniform techniques. Therefore, an accurate analysis of the predictive value of preoperative imaging cannot be made on the basis of their results.

In our series, the resectability rate was higher than that of the series by Jarnagin et al; in our series, lesions in 112 (94.1%) of 119 instances that were considered to be resectable on the basis of helical CT results were successfully resected. However, the results are difficult to compare because of the differences in preoperative imaging techniques and in the definition of nonresectable disease. In our series, nonresectable lesions in three (43%) of seven instances were due to unanticipated hepatic metastases; in three (43%) of seven instances, they were related to extrahepatic disease. Therefore, with our preoperative imaging protocol, seven (5.9%) of the 119 patients underwent un-

necessary laparotomy. These results compare favorably with those of other series (23,24) and were achieved without the use of expensive or invasive procedures such as positron emission tomography, diagnostic laparoscopy, or laparoscopic US.

A limitation of our study was that the use of 5-mm collimation and 10-mm intervals in the examination of the lower abdomen might have been suboptimal. Because of tube-heating limitations, helical acquisition of images in the rest of the abdomen with the use of the standard technique and 300 mAs was usually not possible. However, as all radiologic procedures were closely monitored by one of the attending radiologists, additional images of 5-mm sections with 5-mm intervals were obtained whenever doubt arose in the study of the lower abdomen. Furthermore, our helical acquisition covered the whole upper abdomen from the dome of the lung bases to the iliac crests. Therefore, the majority of possible extrahepatic locations of disease were studied with 5-mm collimation and 5-mm intervals.

Metastatic lesions missed during preoperative work-up or hepatic resection will result in tumor persistence and, consequently, in lower patient survival rates. Although follow-up in our series was short, the 4-year survival rate of 58.6% compares favorably with that of other surgical series (5,7,8); this finding suggests that preoperative metastatic detection was high.

In summary, in our experience, the use of helical CT as the only preoperative imaging technique in the assessment of colorectal cancer metastases allowed accurate preoperative staging (sensitivity, 85.1%; positive predictive value, 96.1%). In addition, 112 (94.1%) of the 119 patients who were considered to be candidates for surgical treatment underwent successful curative resection. In our institution, helical CT has become the routine preoperative imaging technique in patients who are candidates for hepatic resection, due to the noninvasive nature of the examination, its wide availability, and its ability to depict extrahepatic disease.

Acknowledgment: This article is dedicated to the memory of Lluis C. Pons, MD.

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