Radiology of colorectal cancer with emphasis on imaging of liver metastases

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Metastases of Colorectal Carcinoma: Comparison of Soft- and Hard-Copy Helical CT Interpretation

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ABSTRACT

Purpose: To compare soft- and hard-copy computed tomographic (CT) image interpretation with regard to evaluation time and detection rates for hepatic and extrahepatic colorectal metastases in candidates for liver surgery.

Materials and Methods: In 20 patients with a history of colorectal carcinoma, two radiologists independently evaluated CT data sets. Focal hepatic lesions were characterized as benign or malignant by using a five-point scale. In each patient, soft-copy readouts and hard-copy printouts were compared for nonenhanced hepatic, contrast material-enhanced hepatic, and contrast-enhanced extrahepatic data sets. A stopwatch was used to document evaluation time. Ninety-two hepatic metastases and six extrahepatic metastatic recurrences were detected with the standard of reference – surgical, intra-operative ultrasonographic, and histologic findings.

Results: Both observers evaluated the contrast-enhanced hepatic data set significantly faster (P = .026 and .009) by using soft-copy readouts. The contrast-enhanced extrahepatic data set was also evaluated significantly faster (P = .010 and .006) with soft-copy readouts. Detection of hepatic and extrahepatic tumor with soft-copy readouts is not significantly superior to that with hard copies. Detection rates of hepatic metastases for nonenhanced and contrast-enhanced CT for both observers ranged from 50%-80% (46-74 of 92) for soft-copy readouts and 46%-75% (42-69 of 92) for hard copies. Interobserver agreement was highest for contrast-enhanced soft-copy readouts for hepatic metastases.

Conclusion: Soft-copy readouts of contrast-enhanced CT data sets for the detection of hepatic metastases and extrahepatic metastatic recurrences were evaluated significantly faster than were hard copies, with at least equal sensitivity and with excellent interobserver agreement.

INTRODUCTION

Helical computed tomographic (CT) images can be viewed on the screen of a workstation (soft-copy) or on a viewing box (hard-copy). Viewing the CT images on a workstation has potential technical, financial, and perceptual advantages. The workstation enables a radiologist to view the entire data set in a movielike fashion (cine mode). This could activate the motion-processing capabilities of the human visual system, which improves differentiation of tubular (vessels) and spherical (lesions) structures [1]. The workstation also enables the radiologist to alter window and level settings [1-3]. Hard copies of all available images can of course be printed, but in daily practice, this is hardly ever done for practical and financial reasons [3,4]. Furthermore, with the large number of images generated by the helical CT scanner, it might be faster to evaluate soft-copy readouts than to look at all the hard-copy images.

In a MEDLINE search on the comparison of soft- and hard-copy evaluation of CT data sets, we did not find any studies concerning the detection of hepatic metastases. Both experimental and clinical studies [1,3,5,6] have been performed on the differences between soft- and hard-copy interpretation in focal lesion detection, but the lung was used for evaluation. Bonaldi et al [4] performed a study on the pancreas, but the mainstay of their study was anatomy and image quality. Tazawa et al [7] concentrated on display rate and conspicuity of abdominal structures. None of these studies compared evaluation times for soft- and hard-copy interpretation, although assumptions were made that soft-copy evaluation would be faster.

The purpose of the present study was to compare soft- and hard-copy CT interpretation for evaluation time and detection rates for hepatic and extrahepatic colorectal metastases in candidates for liver surgery.

MATERIALS AND METHODS

PATIENTS

Between September 1995 and February 1997, 45 consecutive patients suspected of having colorectal hepatic metastases on the basis of ultrasonographic (US) findings and increased serum levels of tumor markers, such as carcinoembryonic antigen, were eligible for this study. The patients were referred to our hospital for partial liver resection or isolated liver perfusion

with melphalan [8].

In 25 patients the standard of reference was not complete. The main reason was no or limited surgery because of extensive tumor depicted at CT. Thus, 20 patients (12 men, eight women) aged 38-74 years (mean age, 57 years; median age, 58 years) were included in this study. All patients had a history of colorectal adenocarcinoma. Ultimately, one of these patients had multiple hemangiomas, including one giant hemangioma that required surgery. The other 19 patients had at least one histologically proven metastasis to the liver. No patient had relevant comorbidity of the liver, such as cirrhosis or steatosis. The institutional review board of our hospital did not require specific approval or informed patient consent for this study.

The median interval between preoperative CT examination and surgery was 26 days. With the exception of two patients, this interval was less than 9 weeks. In the two remaining patients (with 13 and 17 weeks, respectively, between CT and surgery) in whom progressive disease was excluded by means of repeat CT examination prior to surgery and determination of intra-operative findings, treatment was delayed because of severe pulmonary problems.

HELICAL CT TECHNIQUE

CT was performed with a helical scanner (SR7000 or AVE upgrade; Philips Medical Systems, Best, The Netherlands). Each patient orally ingested 500 ml of contrast agent ((30 ml Telebrix 350; Laboratoire Guerbet, Aulnay-sous-Bois, France) mixed with 1 liter water) within 1 hour prior to CT examination. All scans, both nonenhanced and contrast material-enhanced, were acquired during one breath hold. Field-of-view, tube potential, and current were chosen according to patient habitus, but typically we used a field of view of 350 mm, with 120 kV and 250 mA. Gantry rotation time was 1 second. All images were reconstructed in a 512 x 512 matrix.

First, a nonenhanced acquisition of the liver region (collimation, 5 mm; table increment, 5 mm/sec; reconstruction interval, 3 mm) was performed. After administration of 150 ml of Iomeron 350 (Bracco, Milan, Italy) or Xenetix 300 (Laboratoire Guerbet), the liver was examined again with a fixed delay of 60 seconds relative to the start of injection of the contrast agent (collimation, 3 mm; table increment, 5 mm/sec; reconstruction interval, 3 mm). The contrast agent was delivered with a power injector (Medrad, Pittsburgh, Pa.) at 3 ml/sec via the antecubital vein. After the liver was scanned in the portal venous phase, the patient

was allowed to take a few deep breaths; subsequently, in another breath hold, the remainder of the abdomen was scanned down to the level of the groin (collimation, 7 mm; table increment, 10 mm/sec; reconstruction interval, 5 mm).

STANDARD OF REFERENCE

The standard of reference in all patients was the combination of surgical, intra-operative ultrasound (IOUS), and histologic findings. After inspection of the abdomen and complete mobilization of the liver, the surgeon palpated the liver bimanually. An experienced radiologist (M.E.J.P., with 3 years of experience), with full knowledge of the preoperative data, performed IOUS with an Aloka 2000 system (Aloka, Tokyo, Japan) with a 7.5-MHz transducer tailored for IOUS procedures. Examinations were recorded on videotape. All liver segments were examined for lesions identified preoperatively and for additional lesions.

By using the defined standard of reference, we categorized lesions as either malignant or benign on the basis of histologic findings, consistency at palpation, characteristic appearance, and compressibility at IOUS. Benign lesions were subsequently categorized as hemangioma (hyperechoic, geometrically defined, and compressible at IOUS) or cyst (sharply defined, thin walled, and anechoic with postacoustic enhancement at IOUS). Lesions that did not meet these criteria were considered potentially malignant and were either resected or sampled with preoperative fine-needle aspiration biopsy. We identified 132 focal hepatic lesions: 92 malignant and 40 benign (24 hemangiomas, 15 cysts, and one granulomatous nodule). The median number of lesions per patient was six (range, 1-18). Each lesion was localized by using the Bismuth system [9].

The largest diameter of all lesions was measured with IOUS: 52 lesions (27 malignant and 25 benign) were $\leq$ 10 mm, and 80 lesions (65 malignant and 15 benign) were > 10 mm. The median diameter of all lesions was 16 mm (range, 1.6-130.0 mm).

Extrahepatic tumor was detected during surgery in six patients: Three patients had lymph node metastases, two had peritoneal carcinomatosis, and one had residual primary tumor.

DATA ANALYSIS

Image Analysis

Hard-copy (including all reconstructed images) and soft-copy data sets for all 20 patients were

reviewed independently by two experienced CT radiologists (M.N.J.M.W., with 7 years of experience, and E.C.J., with 4 years of experience). The soft- and hard-copy data sets for individual patients were randomized and reviewed with a time interval of at least 2 weeks. The order of images evaluated in each patient was nonenhanced hepatic, contrast-enhanced hepatic, and finally contrast-enhanced extrahepatic.

An Easyvision workstation (Philips Medical Systems), fitted with a 21-inch monitor with a resolution of 1,600 x 1,200 pixels, was used for soft-copy cine loop evaluation. The cine loop window measured 14.8 x 14.8 cm. The reviewers could freely alter display rate [2] and window and level settings. A standard viewing box (Planilux; Gerätebau F. Schulte, Warstein, Germany), divided into eight independently illuminated fields (one film per field), was used for hard-copy images. The hard copies were printed with a commercially available laser printer (Ektascan 2180; Kodak, Rochester, NY.). Images of 10.4 x 8.1 cm (20 images per film) were supplied with *(a)* a soft-tissue window setting of 300 HU (Hounsfield Units) and level setting of 0 HU for nonenhanced images and 400 and 40 HU, respectively, for contrast-enhanced images; and *(b)* a liver window setting of 100 HU and level setting of 60 HU for nonenhanced images and 170 and 120 HU, respectively, for contrast-enhanced images.

The observer indicated localization, size, confidence level of presence, and suspected nature of each lesion. Localization was recorded according to the Bismuth system [9]. The confidence level was expressed with a three-point scale (1 = definitely present, 2 = probably present, and 3 = possibly present). The suspected nature of each lesion was expressed with a five-point scale (1 = definitely benign, 2 = probably benign, 3 = indeterminate, 4 = probably malignant, and 5 = definitely malignant) on the basis of attenuation, conspicuity, morphology, and contrast enhancement by using previously described criteria [10]. Features associated with benign lesions were uniform hypoattenuation and sharp margins. Round lesions without the presence of solid tissue or definable walls were characterized as cysts. Lobulated shape was regarded as a benign sign (of hemangioma). Absence of contrast enhancement was noted in cysts, whereas peripheral nodular enhancement with variable centripetal filling was regarded as a specific sign of hemangioma.

Features considered to indicate colorectal metastases were areas of variable hypoattenuation within the lesion, amorphous or punctate calcifications (mucinous adenocarcinoma), indistinct margins, irregular shape, and a tendency to confluence. Absence of enhancement or an irregular surrounding enhancing rim were regarded as manifestations of

metastases.

For the 132 lesions identified by using the standard of reference, presence, localization, and suspected nature were compared with reference findings (M.E.J.P.).

Evaluation Time

For each patient, the time an observer needed to analyze each of the three data sets (nonenhanced hepatic, contrast-enhanced hepatic, and contrast-enhanced extrahepatic) was measured with a stopwatch for hard copies and soft-copy readouts. Time measurement was started once a complete data set was available for review; thus, set-up time was not included. The observers stopped time measurement when they were finished with their review. A transcriber made notes of the observer's comments in clinical record form. The total evaluation time for the contrast-enhanced data set was calculated by adding the evaluation times for the contrast-enhanced hepatic and extrahepatic data sets.

Statistical Analysis

Statistical analysis of detection rates was performed for small (≤ 10 mm) and large (> 10 mm) lesions separately and for cumulative data (small and large lesions together). Because of the limited number of detected small lesions, confidence levels, interobserver variability, and receiver operating characteristic (ROC) analyses were performed only for cumulative data. For sensitivity calculations and interobserver variability analysis, a lesion detected on CT images was considered malignant if an observer rated it as definitely malignant (score of 5) or probably malignant (score of 4). Extrahepatic tumor data were not subjected to statistical analysis because of the small data set.

Sensitivities with use of hard copies and soft-copy readouts were compared by using the McNemar test. The Wilcoxon signed-rank test was used to compare the confidence levels with both viewing modes. κ statistics were used to determine interobserver agreement in the detection of hepatic metastases. κ values of 0.00-0.40 were considered to indicate poor correlation; values of 0.41-0.75, good; and 0.76-1.00, excellent [11].

ROC analysis was performed to compare viewing modes for the characterization of lesions. ROC curves were fitted with the use of the maximum likelihood method, as implemented in the CORROC2 program (Metz CE, University of Chicago, Ill.). To enable

statistical comparison of lesion characterization, only lesions detected by each observer with both viewing modes were included in this analysis.

The evaluation times of the various components of the hard copies and soft-copy readouts were compared by using the two-tailed Student *t* test.

For all tests used, a *P* value of less than .05 was considered to indicate a statistically significant difference.

RESULTS

DETECTION OF HEPATIC METASTASES

Sensitivity of both viewing modes for detection of metastases was low for both small lesions and nonenhanced data sets. Detection of hepatic metastases tended to be better with soft-copy readouts than with hard copies (Tables 1, 2).

Table 1. Sensitivity for Hepatic Metastases at Nonenhanced CT.

Lesion Size and Readout Type	Observer 1	Observer 2
≤ 10 mm (n = 27)		
Soft-copy	3 (11.1 [0.0 - 22.9])	2 (7.4 [0.0 - 17.3])
Hard-copy	1 (3.7 [0.0 - 10.8])	1 (3.7 [0.0 - 10.8])
P value[#]	.63	1.0
> 10 mm (n = 65)		
Soft-copy	44 (67.7 [56.3 - 79.1])	44 (67.7 [56.3 - 79.1])
Hard-copy	41 (63.1 [51.4 - 74.8])	45 (69.2 [58.0 - 80.4])
P value[#]	.66	1.0
All (n = 92)		
Soft-copy	47 (51.1 [40.9 - 61.3])	46 (50.0 [39.8 - 60.2])
Hard-copy	42 (45.7 [35.5 - 55.9])	46 (50.0 [39.8 - 60.2])
P value[#]	.42	1.0

Data are number of lesions. Numbers in parentheses are percentages. Values in square brackets are 95% confidence intervals.
[#] *P* values refer to soft- vs. hard-copy.

Table 2. Sensitivity for Hepatic Metastases at Contrast-enhanced CT.

Lesion Size and Readout Type	Observer 1	Observer 2
≤ 10 mm (n = 27)		
Soft-copy	11 (40.7 [22.2 - 59.2])	12 (44.4 [25.7 - 63.1])
Hard-copy	9 (33.3 [15.5 - 51.1])	9 (33.3 [15.5 - 51.1])
P value[#]	.63	.25
> 10 mm (n = 65)		
Soft-copy	63 (96.9 [92.7 - 100.0])	61 (93.8 [87.9 - 99.7])
Hard-copy	59 (90.8 [83.8 - 97.8])	60 (92.3 [85.8 - 98.8])
P value[#]	.29	.99
All (n = 92)		
Soft-copy	74 (80.4 [72.3 - 88.5])	73 (79.3 [71.0 - 87.6])
Hard-copy	68 (73.9 [64.9 - 82.9])	69 (75.0 [66.2 - 83.8])
P value[#]	.15	.34

Data are number of lesions. Numbers in parentheses are percentages. Values in square brackets are 95% confidence intervals.
[#] *P* values refer to soft- vs. hard-copy.

Confidence levels for the detection of hepatic metastases were almost equal for both viewing modes and varied between 1.06 ± 0.24 (hard-copy) and 1.09 ± 0.39 (soft-copy) for observer 1 and between 1.08 ± 0.27 (hard-copy) and 1.13 ± 0.41 (soft-copy) for observer 2.

Interobserver Agreement

κ values for the detection of hepatic metastases of all sizes were excellent for contrast-enhanced soft-copy readouts (κ = 0.83 ± 0.07). κ values were good for soft-copy readouts of the nonenhanced hepatic data set (κ = 0.63 ± 0.08) and for hard copies of both nonenhanced (κ = 0.74 ± 0.07) and contrast-enhanced (κ = 0.74 ± 0.08) hepatic data sets.

Lesion Characterization

Results of ROC analysis for the characterization of focal liver lesions, regardless of size, showed no significant differences in the area under the ROC curve for the soft-copy readouts and hard copies for both observers (Table 3 and Figures 1, 2).

Table 3. ROC Analysis for Characterization of Focal Hepatic Lesions.

Observer	Dataset	n	Soft-Copy[#]	Hard-Copy[#]	*P* Value
1	Nonenhanced	47	0.83 ± 0.10	0.83 ± 0.07	.98
	Contrast-enhanced	80	1.0 ± 0.01	0.99 ± 0.01	.80
2	Nonenhanced	56	0.83 ± 0.10	0.91 ± 0.08	.37
	Contrast-enhanced	87	0.97 ± 0.04	0.98 ± 0.01	.64

[#] Data are areas under the ROC curve ± standard error of mean.
n = number of focal hepatic lesions.

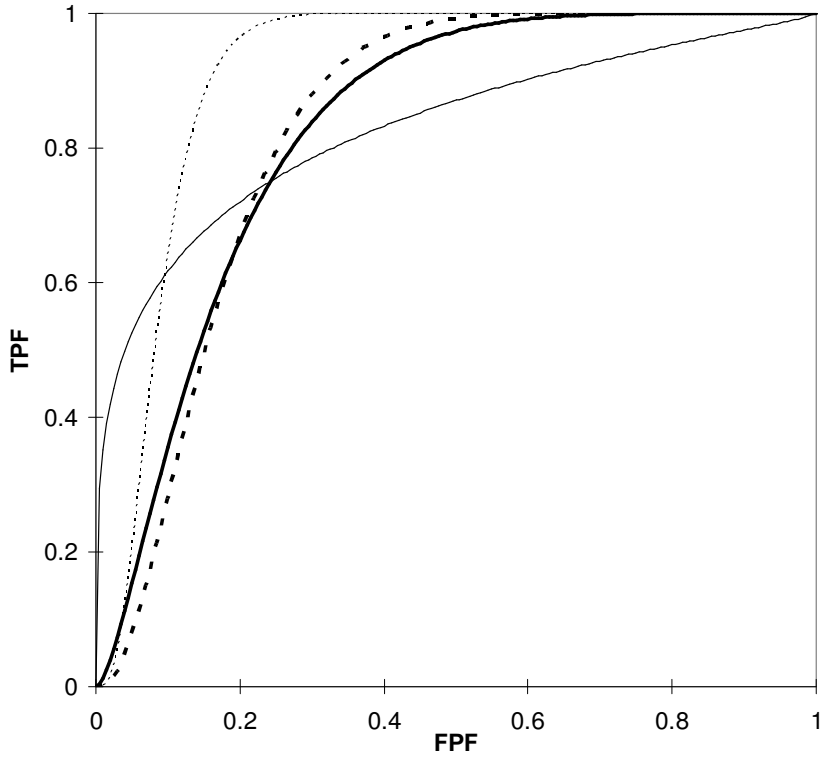

Figure 1. ROC curves for nonenhanced CT.
FPF = false-positive fraction, TPF = true-positive fraction. Thin solid line = observer 1 interpretation of hard copies, thin dotted line = observer 2 interpretation of hard copies, thick solid line = observer 1 interpretation of soft-copy readout, thick dotted line = observer 2 interpretation of soft-copy readout.

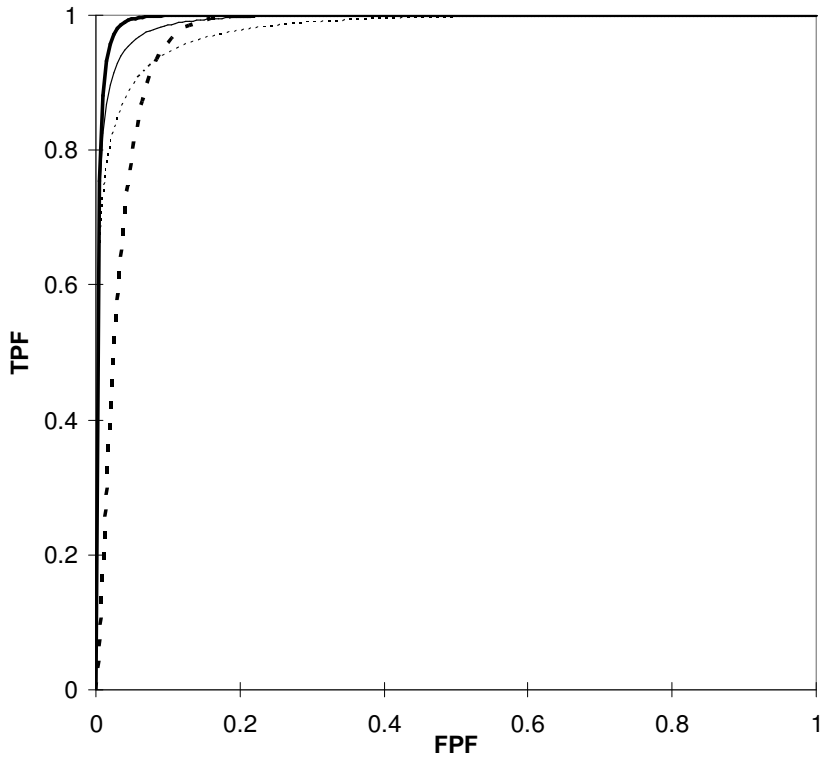

Figure 2. ROC curves for nonenhanced CT.
FPF = false-positive fraction, TPF = true-positive fraction. Thin solid line = observer 1 interpretation of hard copies, thin dotted line = observer 2 interpretation of hard copies, thick solid line = observer 1 interpretation of soft-copy readout, thick dotted line = observer 2 interpretation of soft-copy readout.

EXTRAHEPATIC TUMOR

Observer 1 detected two of six extrahepatic metastatic recurrences on hard copies, compared with four of six on softcopy readouts. Observer 2 detected three of six extrahepatic metastatic recurrences with both viewing modes.

EVALUATION TIME

For both observers, evaluation of the nonenhanced hepatic data set was slightly faster with hard copies than with soft-copy readouts. Both observers evaluated all contrast-enhanced data sets (hepatic, extrahepatic, and combined) significantly faster with soft-copy readouts than with hard copies (Table 4).

Table 4. Evaluation Time.

Observer	Dataset	Soft-copy[#]	Hard-copy[#]	*P* Value
1	Nonenhanced hepatic	155	147	.473
	Contrast-enhanced hepatic	151	201	.026
	Contrast-enhanced extrahepatic	111	155	.010
	Contrast-enhanced combined	262	356	.001
2	Nonenhanced hepatic	108	96	.218
	Contrast-enhanced hepatic	153	192	.009
	Contrast-enhanced extrahepatic	71	107	.006
	Contrast-enhanced combined	224	299	< .001

[#] Data are mean evaluation times per data set in seconds for 20 patients.

DISCUSSION

The evaluation time of soft-copy readouts for the contrast-enhanced hepatic data set, which is generally regarded as the most important CT data set in the detection of colorectal hepatic metastases, was significantly shorter (P = .026 and .009) for both observers than that for hard copies. The shorter evaluation time for hard copies of the nonenhanced data set is rather difficult to explain. We think that the observers tried to overcome the known limited sensitivity of the nonenhanced data set by making optimal use of features of the viewing station. Repeated runs of the cine loop with different window and level settings were used frequently.

Sensitivity for hepatic metastases and confidence levels for detection are somewhat higher with soft-copy readouts but not significantly so. Observer agreement for the detection of hepatic metastases was highest with soft-copy readouts for the contrast-enhanced hepatic data set. These data are in accordance with the superior results of using soft-copy readouts for evaluation of pulmonary nodules [1,3,5] and pancreatic lesions [4]. We believe this increased sensitivity for hepatic metastases at soft-copy evaluation is caused by perceptual factors [1,2], image size, and free choice of display rate and window and level settings. Although both observers were free in their choice of viewing distance to compensate for image size, we agree with Seltzer et al [12] that the larger image size of the soft-copy readout is advantageous in tumor detection. The free choice of display rate and window and level settings during softcopy evaluation enabled the observers to adjust these settings to their own preferences, which

therefore might have improved performance.

In candidates for liver surgery, characterization of focal liver lesions is also important. ROC analysis shows similar results for both viewing modes for both observers.

Three limitations might be applicable to this study – first, the larger image size of soft-copy readouts compared with that of hard copies. On the other hand, this study was conducted in a clinical setting, and in those circumstances, the soft-copy image is larger than the hard-copy, and printing hard copies at a size equal to the soft-copy readout would be impractical. Second, in our daily routine, we do not print all reconstructed images, as is probably the case in most departments. In this study, however, we printed all images on film and therefore increased the number of images to be reviewed as hard copies, which thus extended the hardcopy evaluation time. Third, since the nonenhanced hepatic images were evaluated prior to contrast-enhanced hepatic images, lesion detection on contrast-enhanced hepatic images could be influenced. If so, we think this effect is minimal, since detection of colorectal metastases is known to be far superior on portal venous contrast-enhanced hepatic images than on nonenhanced hepatic images.

In summary, soft-copy evaluation for contrast-enhanced CT data sets for the detection of colorectal hepatic metastases and extrahepatic metastatic recurrence is significantly faster than evaluation of hard copies, and interobserver agreement for soft-copy readouts is higher. The detection of hepatic metastases and extrahepatic metastatic recurrences with soft-copy readouts is at least as good as that with hard copies.

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