Predictive Value of Pattern Classification 24 Hours after Radiofrequency Ablation of Liver Metastases on CT and Positron Emission Tomography/CT

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ABSTRACT

Purpose: To assess a classification scheme for predicting local tumor progression (LTP) after radiofrequency (RF) ablation of liver metastases, using predefined patterns on contrast-enhanced computed tomography (CT) and positron emission tomography (PET) combined with CT (PET/CT) acquired 24 hours after RF ablation.

Materials and Methods: There were 45 metastases in 20 patients treated. After 24 hours, imaging of the ablation zones was performed with contrast-enhanced PET/CT. Three independent radiologists prospectively assessed contrast-enhanced CT and combined PET/CT images to identify three patterns: pattern I, no tissue enhancement or fluorodeoxyglucose uptake between the ablation zone and the liver parenchyma; pattern II, a rimlike pattern; and pattern III, a peripheral nodule. PET/CT images obtained after 8–10 weeks were evaluated for LTP. The patterns were analyzed for their sensitivity, specificity, positive predictive value, and negative predictive value for predicting LTP.

Results: Pattern I was most frequently observed (81% for contrast-enhanced CT and 61% for PET/CT) as well as for ablation zones that showed LTP (52% and 37%, respectively). Conversely, pattern II was observed for tumors that were completely ablated (6% and 29%, respectively). Patterns II and III together had the highest sensitivity for predicting LTP (48% and 63%, respectively); pattern III had the highest specificity (94% and 95%, respectively). For nodular patterns, test characteristics were better for PET/CT compared with contrast-enhanced CT, but the difference was not significant. Nodular patterns > 1 cm achieved high positive predictive value (both 100%).

Conclusions: Inflammation and hyperemia can hinder interpretation on imaging 24 hours after RF ablation, especially on PET/CT. Nodular patterns around the ablation zone on early contrast-enhanced CT and PET/CT have a high predictive value for LTP and should be taken into account for disease management.

ABBREVIATIONS

FDG = fluorodeoxyglucose, LTP = local tumor progression, NPV = negative predictive value, PPV = positive predictive value

Local tumor progression (LTP) remains a concern after radiofrequency (RF) ablation, particularly in tumors > 3 cm (1–5). LTP is typically caused by incomplete ablation secondary to incorrect placement of the probe, a heat sink effect owing to the proximity of large vessels, or a large tumor size (1.5–7). Residual tumor that appears after RF ablation can be treated with repeat ablation when the diameter does not exceed the established size limits of the technique (8). Early identification of residual tumor after RF ablation can facilitate timely retreatment.

During follow-up, contrast-enhanced computed tomography (CT) can be combined with fluorodeoxyglucose (FDG) positron emission tomography (PET) to identify residual tumor effectively (9). PET has shown higher accuracy than contrast-enhanced CT for detecting LTP in follow-up examinations of patients treated with RF ablation (2,10–12). Morphologic imaging modalities have been shown to have limited ability to differentiate
between intervention-induced tissue changes and residual tumor (11,13,14). The question of how much time is required for local hyperemia and inflammation to develop around the ablated tumor remains unresolved. Purandare et al (14) suggested that the ideal time frame for performing a PET/CT scan is 24–48 hours after the ablation because at that time, FDG uptake caused by the inflammation is not yet apparent.

Many authors have described patterns on CT and combined PET/CT images obtained after treatment that appeared at the interfaces between the ablation zone, the ablative margin, and the surrounding liver parenchyma (13,15,16). To our knowledge, no standardized study has described the patterns that appeared in the ablation zone at 24 hours after RF ablation of liver metastases. In this article, imaging assessments performed at 24 hours after ablation are referred to as early assessments. The purpose of this prospective study was to assess the predictive value of predefined patterns identified on early contrast-enhanced CT and PET/CT images for predicting technique effectiveness, defined as the absence of LTP on PET/CT images acquired at the first follow-up examination performed 8–10 weeks after RF ablation.

**MATERIALS AND METHODS**

**Patient Population**

Between July 2008 and January 2010, patients with a known history of malignancy and a clinical indication for RF ablation were consecutively included in this prospective, single-center, nonrandomized study. The primary inclusion criterion was the presence of at least one unresectable liver metastasis, regardless of the primary tumor histology. These index tumors were defined as malignant either by a combination of typical radiologic characteristics and the presence of a known primary tumor or by histologic confirmation. Other inclusion criteria were the presence of focal FDG uptake in the tumor detected on a PET/CT scan performed within 1 month before the intervention. Exclusion criteria were hyper-vascularity of the metastases detected on the arterial phase of CT or magnetic resonance imaging and all established contraindications applicable at our institution for RF ablation, such as a maximum of five focal index tumors with a maximum diameter of 5 cm. There were 23 patients who met the inclusion criteria in this study. One follow-up PET/CT scan was performed in another hospital without intravenous administration of iodine contrast material. Three patients were excluded from evaluation because of information lost during follow-up. Data from the remaining 6 men and 14 women were considered eligible for analysis.

There were 45 unresectable hypovascular liver metastases included. The median patient age was 62 years (mean, 64.5 y; range, 42–87 y). Patients had sustained liver metastases from colorectal carcinoma (n = 16), melanoma (n = 3), or breast carcinoma (n = 1). The average number of metastases per patient was 2.25 (range, 1–5). The 45 metastases ranged from 6–41 mm in diameter (mean, 18.6 mm; median, 18 mm). The institutional Ethics Committee approved the study, and all patients gave written informed consent.

**Study Protocol**

The protocol comprised four procedures as follows: (a) a whole-body PET/CT scan within 1 month before RF ablation; (b) RF ablation procedure; (c) a liver-only contrast-enhanced PET/CT scan performed 24 hours after RF ablation; and (d) a whole-body contrast-enhanced PET/CT scan performed 8–10 weeks after the procedure.

**Percutaneous RF Ablation Procedure**

All RF ablation procedures were performed with the Cool-tip RF ablation device (100 W RF 2000 generator; Covidien, Sunnyvale, California) by one interventional radiologist with 12 years of experience. The electrodes were inserted into the tumor under CT fluoroscopic guidance (SOMATOM Emotion 16; Siemens Healthcare, Erlangen, Germany). When required, the electrodes were repositioned during the procedure to ensure effective ablation of the tumor (17). RF energy was applied for at least 10–12 minutes and was impedance regulated. The treatment was stopped when a temperature of at least 55°C was achieved at the needle tip, after switching off the RF current and the internal cooling. All ablations were performed under general anesthesia.

**Imaging**

Patients fasted for at least 4 hours before administration of FDG. To minimize artifacts over the liver, patients raised their arms above their head when possible. All PET/CT scans were acquired during shallow breathing with a GEMINI TF 64 camera (Philips Medical Systems, Cleveland, Ohio). PET imaging started at 60 minutes ± 5 after intravenous administration of FDG (activities ranging from 250–300 MBq). CT data (120 kV, 64 × 0.625 mm, 0.75-second tube rotation time, pitch 0.83, dose modulation according to patient attenuation at every table position with z-dose modulation) were acquired in the venous phase, starting 90 seconds after intravenous administration of 100–120 mL iodinated contrast material, iopromide (Ultrasave 370; Bayer HealthCare, Berlin, Germany). The ablation zones were scanned in the venous phase owing to the hypovascular nature of the selected index tumors. PET data were subsequently acquired at 1 minute per bed position. CT images were reconstructed with slice thicknesses of 2 mm for axial views and 4 mm for coronal views. PET images were reconstructed with an iterative algorithm (BLOB-OS, 3 iterations, 33 subsets). The reconstructed
emission data were corrected for scatter and attenuation based on CT-derived attenuation correction factors.

**Data Interpretation**

Three board-certified abdominal radiologists with 4, 6, and 7 years of experience (all with 4 years of experience in reading PET/CT images), who were not involved in the RF ablation procedure, performed a blinded review of the images acquired 24 hours after RF ablation. The review was performed in two separate sessions—first contrast-enhanced CT images and then combined PET/CT images; in the latter session, the contrast-enhanced CT images could also be viewed separately. A 5-week interval was applied between sessions to avoid memory-induced bias. Readers reviewed the images on a picture archiving and communication workstation (IMPAX DS3000; Agfa, Mortsel, Belgium) with calibrated displays. Various tools were available for the assessments, including window-level and density measurements. The PET/CT scans acquired in the month before the RF ablation procedure were available for comparison with the index tumors.

All images were evaluated for zones of tissue enhancement (contrast-enhanced CT) and tracer uptake (PET) between the ablation zone and the liver parenchyma. For this purpose, the readers were provided with a classification scale consisting of predefined image patterns (Fig 1). The patterns occupied an area between the ablation zone and the surrounding liver parenchyma (shown in black in Fig 1) and were based on our previous experience and on similar patterns previously published to describe follow-up imaging after RF ablation of liver tumors (14,18–24). Five classes were implemented to capture variations in the three main patterns: pattern I, no tissue enhancement or FDG uptake between the ablation zone and liver parenchyma; pattern II, rimlike tissue enhancement or FDG uptake, with or without interruption; pattern III, nodular peripheral attenuation or FDG uptake, small or large. We used subdivisions for patterns II and III, distinguishing smooth (IIa) or irregular (IIb) patterns and small (IIIa) or large (IIIb) nodes with diameters < 1 cm or > 1 cm, respectively.

LTP was evaluated based on the PET/CT scan acquired at 8–10 weeks after the RF ablation procedure; this was the first routine clinical follow-up in our institution. The interpretation was established by consensus between two radiologists who had not participated in the assessments of images acquired at 24 hours after RF ablation, through comparison of images acquired before and after ablation. LTP was defined by the presence of areas with focal, nodular FDG uptake at the periphery of the ablation zone (2,25). Complete ablation (no LTP) was defined as the absence of new foci (26).

**Pattern Assessments**

The pattern assignments determined on contrast-enhanced CT and PET/CT images were compared by calculating the linearly weighted $\kappa$, which takes into account the frequencies of agreement between imaging modalities and the extent of disagreement (27). The calculation was performed for each observer and averaged over the observers to obtain an overall $\kappa$ and corresponding SE. In a similar fashion, we assessed the overall agreement between the observers for each modality.

Patterns were classified into groups based on whether the ablation zones exhibited LTP at the 8-week follow-up. The frequencies of patterns in the LTP and no-LTP groups were compared with Fisher exact test. This statistical test was performed for each observer separately. The obtained $P$ values for each observer were combined into an overall $P$ value based on Fisher method for combining $P$ values and assessed with $\chi^2$ distribution and 6 degrees of freedom. This procedure produces a conservative estimate.

**Accuracy and Predictive Value**

The diagnostic value of the different patterns was evaluated by deriving four tests for predicting the development of LTP by combining the patterns into categories. The tests are shown in Table 1. Test I considers all ablation zones with pattern I as completely ablated (no LTP), and other patterns are thought to represent LTP. Similarly, tests IIa, IIb, and IIIa were defined as shown in

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**Figure 1.** Predefined patterns included in the liver tumor ablation classification scheme. These five classes were assigned to contrast-enhanced CT and PET/CT images according to the pattern of the tissue enhancement or increased FDG uptake (black) detected at the margin between the ablation zone (white) and the surrounding normal liver parenchyma (grey). Pattern I, no attenuation difference or FDG uptake; pattern II, regular (IIa) or irregular (IIb) rim of distinct attenuation or FDG uptake; pattern III, nodular attenuation difference or FDG uptake, including small nodes (IIIa) and large nodes (IIIb), with diameters < 1 cm or > 1 cm, respectively.
Table 1. Definitions of Thresholds for Different Diagnostic Tests

<table>
<thead>
<tr>
<th>Pattern</th>
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<tbody>
<tr>
<td>Test I</td>
<td>No LTP</td>
<td>LTP</td>
<td>LTP</td>
<td>LTP</td>
<td>LTP</td>
</tr>
<tr>
<td>Test IIa</td>
<td>No LTP</td>
<td>No LTP</td>
<td>LTP</td>
<td>LTP</td>
<td>LTP</td>
</tr>
<tr>
<td>Test IIb</td>
<td>No LTP</td>
<td>No LTP</td>
<td>No LTP</td>
<td>LTP</td>
<td>LTP</td>
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<tr>
<td>Test IIIa</td>
<td>No LTP</td>
<td>No LTP</td>
<td>No LTP</td>
<td>No LTP</td>
<td>LTP</td>
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<tr>
<td>Pattern I</td>
<td>No LTP</td>
<td>LTP</td>
<td>LTP</td>
<td>LTP</td>
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<tr>
<td>Pattern IIa</td>
<td>No LTP</td>
<td>No LTP</td>
<td>LTP</td>
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<tr>
<td>Pattern IIb</td>
<td>No LTP</td>
<td>No LTP</td>
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<tr>
<td>Pattern IIIa</td>
<td>No LTP</td>
<td>No LTP</td>
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Note. Patterns (defined in Fig 1) were identified at 24 hours after RF ablation.

LTP = long-term progression of liver metastasis, detected at 8–10 weeks after RF ablation.

RESULTS

Of 45 ablation zones, 9 (20%) were determined to have LTP; the other 36 (80%) showed no tumor manifestation on PET/CT after 8–10 weeks. Representative images are shown in Figures 2a–c, 3a–c, and 4a,b. Of the nine ablation zones (in eight patients) that showed LTP, six patients received repeat RF ablation. One patient with two ablation zones that showed LTP underwent stereotactic radiotherapy. One patient with new extrahepatic disease was treated with chemotherapy. Two index tumors that were considered to be completely ablated after 8–10 weeks demonstrated LTP on PET/CT during later follow-up (18 weeks and 28 weeks after RF ablation).

Pattern Distributions

Figure 5 shows the frequency distribution of the patterns found in all ablation zones pooled over all observers. Overall, regardless of outcome, pattern I (Fig 5) was observed most often, and it was identified more often in contrast-enhanced CT images (81%) than in PET/CT images (61%). Patterns IIa and IIIb were rarely observed on either contrast-enhanced CT images (3% and 1%, respectively) or PET/CT images (2% for each pattern). The linearly weighted \( \kappa \) for comparing between contrast-enhanced CT and PET/CT image results indicated fair agreement between the pattern assignments (overall \( \kappa = 0.27, SE = 0.02 \)). The overall agreement between observers was fair for contrast-enhanced CT (overall \( \kappa = 0.27, SE = 0.03 \)) and moderate for PET/CT (overall \( \kappa = 0.47, SE = 0.03 \)).

Table 2 shows the frequency distributions of the patterns found in ablation zones with or without LTP at the 8-week follow-up, pooled over all observers. The same data are shown in Figure 6, but only the main patterns are shown because of the low incidences in some subdivisions. Regardless of LTP outcome, most ablation zones were classified as pattern I with both imaging modalities. Pattern I was noted more often for the ablation zones without LTP than for the zones with LTP; the difference was significant for PET/CT images (overall \( P < .024 \)) but not for contrast-enhanced CT images (overall \( P > .022 \)).

Pattern III was identified in only 6% and 5% of ablation zones without LTP in contrast-enhanced CT and PET/CT images, respectively. Pattern IIIb did not occur in ablation zones without LTP. For ablation zones with LTP, pattern III was identified more frequently in PET/CT images (26%) than in contrast-enhanced CT images (15%), but this difference was not statistically significant (overall \( P > .38 \)).

Accuracy and Predictive Value

The predictive values of contrast-enhanced CT and combined PET/CT scans were evaluated with diagnostic tests (Table 3), where the sensitivity, specificity, PPV, and NPV were determined for predicting LTP. The highest sensitivities for LTP were found in test I, and the highest specificities were found in test IIIa. The sensitivity of contrast-enhanced CT in test I was low compared with PET/CT because of the high number of false-negative findings in ablation zones classified as pattern I. Conversely, a high specificity was observed for contrast-enhanced CT in test I because of the high fraction of true-negative findings in ablation zones categorized as pattern I. Both of these results could be explained by the high number of pattern I findings for contrast-enhanced CT.

With tests IIb and IIIa, high specificities (\( \geq 94\% \)) were obtained for both imaging modalities. In other words, when a nodular pattern was detected around the coagulation necrosis, it was a highly specific indicator of LTP. For latter tests, PET/CT images provided higher sensitivity, specificity, PPV, and NPV values than contrast-enhanced CT images, but the difference between imaging
modalities was not significant (overall $P > .05$). When a nodule $> 1$ cm was detected (test IIIa), PPV reached 100% for both imaging modalities. However, this result should be interpreted with caution because we must take into account the low frequency of detecting such nodules in this study.
In this study, we evaluated the value of the patterns seen on imaging after 24 hours for predicting technique effectiveness as evidenced after the prospectively defined time point of 8–10 weeks (28). The rationale for this time point was to assess the added value and potential clinical impact of imaging after 24 hours with respect to the first follow-up as routinely performed in our institution. Based on follow-up PET/CT images acquired at 8–10 weeks after RF ablation, 20% of liver metastases developed LTP. This primary effectiveness rate was comparable to effectiveness rate found in other studies (5,10,29).

**DISCUSSION**

In this study, we evaluated the value of the patterns seen on imaging after 24 hours for predicting technique effectiveness as evidenced after the prospectively defined time point of 8–10 weeks (28). The rationale for this time point was to assess the added value and potential clinical impact of imaging after 24 hours with respect to the first follow-up as routinely performed in our institution. Based on follow-up PET/CT images acquired at 8–10 weeks after RF ablation, 20% of liver metastases developed LTP. This primary effectiveness rate was comparable to effectiveness rate found in other studies (5,10,29).
For both imaging modalities, pattern I was identified at 24 hours after ablation more often in ablation zones without LTP than in zones with LTP. This finding was significant for the PET/CT imaging modality. In comparison, Langenhoff et al (12) studied 56 ablation zones, and 51 (91%) became photopenic on PET images.

Figure 4. Transverse contrast-enhanced CT, PET, and PET/CT images of a solitary metastasis of a colorectal carcinoma in a 42-year-old man. (a) Images obtained 1 week before therapy show the metastasis as a well-described hypodensity on contrast-enhanced CT image and as intense FDG uptake on PET and PET/CT images (arrow). (b) Images acquired 24 hours after RF ablation show the avascular ablation zone; focal FDG uptake was found at the medial border of the RF-treated area (arrow). Ablation of this residual tumor was repeated, and no reactivation was detected over a period of 18 months.

Figure 5. Fractional frequency distributions of the patterns identified in all 45 ablation zones at 24 hours after RF ablation. Bars represent readings from the three evaluators of contrast-enhanced CT (dark) and PET/CT (light) images. CECT = contrast-enhanced CT. (Available in color online at www.jvir.org.)
acquired within 3 weeks of ablative therapy; none of those developed LTP during follow-up. Ryan et al (30) performed PET/CT immediately after ablation to assess technical success. Of 29 ablation zones, 28 (97%) showed no activity on PET, of which 2 (7%) showed LTP during follow up.

The incidence of pattern II in the group without LTP was significantly higher on PET/CT than on contrast-enhanced CT images within 24 hours after RF ablation (29% and 6%, respectively). This inflammatory rim observed after 24 hours can hamper the detection of residual tumors on PET/CT images (31). These results contradict the suggestion from Purandare et al (14) that PET/CT does not show inflammation early after RF ablation. In an animal study that compared multiple imaging modalities in 19 healthy porcine livers, no rimlike areas with increased glucose metabolism were observed on PET/CT images acquired immediately after RF ablation (13). However, rimlike FDG uptake was observed at 3 days to 6 months after the ablation (31). Nevertheless, immediate control with PET/CT imaging after RF ablation under general anesthesia is not practical in clinical situations.

In the present study, the formation of a nodular pattern (pattern III) around the coagulation necrosis was a highly specific indication of LTP. This finding corresponded well to results from a previous study that examined 20 ablation zones with PET/CT imaging after 24 hours; in the study, focal uptake was detected in all three cases of LTP (32). Other investigators reported that signs of LTP can be detected earlier on PET images than on contrast-enhanced CT images acquired in the follow-up period after RF ablation (2,10,12,33). In the present study, LTP was predicted more often with early PET/CT than with early contrast-enhanced CT imaging (26% vs 15%), but the difference was not significant, and they showed similar false-positive rates (6% vs 5%).

For both contrast-enhanced CT and PET/CT, the sensitivity decreased, and the specificity increased gradually from tests I to IIIa. This finding suggested that the proposed pattern ranking corresponded to a progressively increasing risk of LTP occurrence. The high NPV of

<table>
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<tr>
<th>Table 2. Pattern Distributions on Contrast-Enhanced CT and PET/CT Images That Showed No LTP or LTP Pooled over All Observers</th>
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<tbody>
<tr>
<td><strong>No LTP (n = 36 Tumors)</strong></td>
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<tr>
<td><strong>Contrast-Enhanced CT</strong></td>
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<tr>
<td>Pattern I</td>
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<td>Pattern IIa</td>
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<tr>
<td>Pattern IIb</td>
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<tr>
<td>Pattern IIIa</td>
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<td>Pattern IIIb</td>
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Note. The percentages were rounded; in some cases, this resulted in totals apparently > 100%.

CT = computed tomography; LTP = local tumor progression of liver metastasis, evaluated on follow-up PET/CT images acquired at 8–10 weeks after ablation; PET/CT = positron emission tomography combined with contrast-enhanced CT.
test I (> 87% for both modalities) indicated that when no attenuation difference or FDG uptake is detected early, there is a high chance of complete ablation. The PPV of test IIb was 40% for contrast-enhanced CT and 58% for PET/CT images. These results suggested that PET/CT was superior to contrast-enhanced CT for predicting LTP. However, the difference between modalities was again not significant. In both modalities, test IIb had relatively low PPVs; it is inadequate for use as a clinical indication of unablated residual tumors. Consequently, we cannot recommend immediate repeat ablation of all nodular patterns. However, a shorter follow-up time is advisable for focal nodules < 1 cm (pattern IIIa), and repeat ablation should be performed immediately for focal nodules > 1 cm (pattern IIIb) (Fig 4a,b).

This study has some limitations. First, the numbers of included patients (n = 20) and index tumors (n = 45) were relatively small. However, these numbers were comparable to numbers reported in other studies that evaluated imaging modalities for the detection of LTP after RF ablation. Second, CT imaging was performed in the venous phase at 90 seconds without bolus tracking, which may have caused variation in enhancement patterns. Third, no biopsy specimens of the LTP were available, and no correlation could be made between the PET/CT images acquired after 8–10 weeks and the histopathology.

In conclusion, we classified the patterns detected on contrast-enhanced CT and PET/CT images acquired 24 hours after RF ablation of focal liver metastases and evaluated their value for predicting LTP demonstrated at the first follow-up examination. The total absence of tissue enhancement or FDG uptake between the ablation zone and liver parenchyma was the most frequently observed pattern. This pattern was also frequently seen in ablation zones that showed LTP after 8–10 weeks. Conversely, for many index tumors that were completely ablated, circumferential FDG uptake was observed within 24 hours after ablation, corresponding to early inflammation and potentially hindering the interpretation of PET/CT images. In contrast, a focal, nodular pattern around the ablation zone has a high predictive value for LTP. We recommend a shortened follow-up time for nodules with diameters < 1 cm detected after 24 hours and immediate repeat ablation for larger nodules. Our study did not show a significant benefit of adding FDG-PET to contrast-enhanced CT imaging to predict the outcome of liver metastases within 24 hours after RF ablation.

### Table 3. Diagnostic Accuracy of Test Pattern Groups Based on Contrast-Enhanced CT and PET/CT Images

<table>
<thead>
<tr>
<th>Test</th>
<th>Contrast-Enhanced CT</th>
<th>PET/CT</th>
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<tbody>
<tr>
<td>Test</td>
<td>Sensitivity</td>
<td>Specificity</td>
</tr>
<tr>
<td>I</td>
<td>48% (4%)</td>
<td>89% (3%)</td>
</tr>
<tr>
<td>IIA</td>
<td>37% (10%)</td>
<td>90% (2%)</td>
</tr>
<tr>
<td>IIb</td>
<td>15% (7%)</td>
<td>94% (3%)</td>
</tr>
<tr>
<td>IIIa</td>
<td>4% (4%)</td>
<td>100% (0%)</td>
</tr>
</tbody>
</table>

Note. Test I, pattern I vs patterns II–III; test IIA, patterns I–IIa vs patterns IIb–II; test IIb, patterns I–IIb vs patterns II and IIB; test IIIa, pattern I–II vs pattern IIb (Table 1). Reported measures are the mean over all observers (and SE), in which values of PPV not defined were omitted.

CT = computed tomography; NPV = negative predictive value; PET/CT = positron emission tomography combined with contrast-enhanced CT; PPV = positive predictive value.

### REFERENCES


27. Cohen J. Weighted kappa: nominal scale agreement with provision for scaled disagreement or partial credit. Psychol Bull 1968; 70:213–220.


