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Relation	


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Preoperative PET-CT is useful for predicting recurrent extrahepatic metastasis of hepatocellular carcinoma after resection

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Abstract

***Purpose*:** In recent years, it has been reported that use of ^{18}F-FDG PET-CT can reveal the degree of hepatocellular carcinoma malignancy. We evaluate the ability of a preoperative ^{18}F-FDG PET-CT to predict the recurrence of extrahepatic metastasis after surgery.

***Methods*:** We retrospectively examined 67 patients who received ^{18}F-FDG PET-CT prior to curative hepatic resection between April 2010 and March 2016. Multivariate Cox regression analysis was performed to identify the factors associated with recurrence of extrahepatic metastasis after surgery. We also evaluated the sensitivity, specifity, positive predictive value, negative predictive value and accuracy of diagnosis of ^{18}F-FDG PET-CT for recurrent extrahepatic metastasis after surgery.

Results: The multivariate analysis identified a tumor-to-normal liver standardized uptake value ratio (TNR) ≥ 1.53 (hazard ratio [HR], 0.037; P = 0.003), multiple tumor nodules (HR, 0.121; P = 0.007), and presence of microvascular invasion (HR, 0.094; P = 0.003) as independent predictors of distant metastasis recurrence. A TNR ≥ 1.53 showed a sensitivity of 91.7%, specificity of 76.4%, positive predictive value of 45.8%, negative predictive value of 97.7%, and accuracy of 79.1% for diagnosing distant metastasis recurrence. In a binomial logistic regression analysis of tumor factors associated with a TNR ≥ 1.53, poor tumor differentiation and large tumor size were significant factors.

***Conclusion*:** ^{18}F-FDG PET-CT and microvascular invasion may be useful for predicting the recurrence of extrahepatic metastasis after surgery.

Key words: PET-CT; Hepatocellular Cancer; recurrence; metastasis

Abbreviations

GLUT1, glucose transporter 1; G6Pase, glucose-6-phosphatase; HK2, hexokinase 2; OR, odds ratio; HR, hazard ratio; SN, simple nodular; non-SN, non-simple nodular; TNR, tumor-to-normal liver standardized uptake value ratio; HBV, hepatitis B virus; HCV, hepatitis C virus; NBNC, patients negative for both HBs antigen and HCV antibody; AFP, α-fetoprotein; AFP-L3, lens culinaris agglutinin a-reactive α-fetoprotein; DCP, des-γ-carboxyprothrombin; CI, confidence interval

Introduction

HCC is a common disease worldwide [1]. Since HCC is associated with intrahepatic metastasis and multicentricity, recurrence is often a problem. Therefore, risk assessment of HCC recurrence is useful for selection of the treatment method and follow-up after treatment. A high α-fetoprotein (AFP) level, non-simple nodular (SN) type, multiple tumors and pathological microvascular invasion (MVI) have been identified as risk factors for early recurrence in surgical cases [2,3,4,5]. It was also reported that postoperative extrahepatic metastasis recurrence tends to occur more frequently in cases with portal invasion and advanced stage [6]. However, no preoperative predictive factors for postoperative extrahepatic metastasis recurrence have been established. If the risk of recurrence of extrahepatic metastasis can be evaluated preoperatively, it would provide useful information for selecting adjuvant therapy [7,8,9,10] and the surgical procedure.

In Japan, since 2010, the national health insurance system has covered the use of PET-CT for all malignant tumors except early stomach cancer, and PET-CT is performed to evaluate HCC. In general, HCC is reported to have poor fluorodeoxyglucose (FDG) uptake because of low glucose transporter 1 (GLUT1) and high glucose-6-phosphatase (G6Pase) expression [11], but strong uptake is sometimes observed. In recent years, studies have shown that FDG

uptake in HCC is useful for predicting MVI, non-SN type HCC, and the degree of tumor differentiation [12,13,14,15,16], as well as measuring the effect of treatment [17,18]. The utility of PET-CT may broaden in the future [18]. The case of our hospital is shown in figure1. This is a 30 mm single HCC case of liver S6. Preoperative PET-CT showed strong uptake of FDG, suggesting a low degree of differentiation. Hepatic resection was performed, but multiple lymph node metastasis occurred after 3 months. In this study, we evaluated the ability of fluorine-18 (^{18}F) FDG PET-CT to diagnose extrahepatic metastasis recurrence after surgery compared with other tests.

Materials and methods

Patients

A total of 67 patients who received curative hepatic resection between April 2010 and March 2016 at Hiroshima University Hospital were enrolled in this study. The inclusion criteria were as follows: (1) diagnosis of HCC confirmed by postoperative pathological examination, (2) preoperative ^{18}F-FDG PET-CT during evaluation of hepatic resection, (3) initial or recurrent HCC with more than 2 years since last treatment (in patients with multiple HCCs, the main tumor was subjected to analysis), (4) there is no intrahepatic recurrence before recurrence of extrahepatic metastasis, and (5) follow up of more than 2 years after resection or the first recurrence of extrahepatic metastasis. Finally, 67 patients met these criteria and were included in the present retrospective study (figure 2). The study was approved by the ethics committee of each hospital and conformed to the 1975 Declaration of Helsinki.

^{18}F-FDG PET-CT Studies and Analysis

^{18}F-FDG PET-CT studies were performed using a three-dimensional combined PET-CT scanner (Biograph mCT; Siemens AG). All patients fasted for at least 4 hours before ^{18}F-FDG

administration and rested quietly for at least 1 hour before PET-CT. The serum glucose level was measured before ^{18}F-FDG administration, and a level less than 150 mg/dL was confirmed.

The ^{18}F-FDG dose was based on patient weight (3.7 MBq/kg) and ranged from 150 to 350 MBq. Low-dose nonenhanced CT imaging was performed for attenuation correction and anatomic localization. PET images were acquired from the base of the skull to the thighs and captured for each bed position for 1.5–6 minutes. All images were reconstructed using an ordered subset expectation maximization method.

The SUVmax was obtained by dividing the maximum activity concentration in the lesion (Bq/g) by the administered activity (Bq) per body weight (g) for semiquantitative evaluation. For patients with multiple tumors, the SUVmax of the largest lesion was used for statistical analysis. Tumor FDG avidity was measured by tumor-to-normal liver standardized uptake value ratio (TNR). TNR was calculated using the following equation: TNR = maximum SUV of the tumor / mean SUV of the normal liver. The amount of ^{18}F-FDG uptake was evaluated by the same skilled radiologist.

Pathological examination

The specimens were examined by independent pathologists. The number and size of the tumors, tumor differentiation, macroscopic classification, MVI, intrahepatic micrometastasis, and tumor stage were evaluated. We defined tumor size as the maximum diameter of the resected tumor specimen. Tumor differentiation, macroscopic classification, and pathological tumor stage were determined histologically according to the classification proposed by the General Rules of the Clinical and Pathological Study of Primary Liver Cancer in Japan [19]. When different tumor grades were found within the same tumor, the most advanced grade was used in the analysis.

Statistical analysis

The cumulative recurrence rate according to each prognostic factor evaluated was plotted using Kaplan–Meier curves, and the differences between curves were assessed for statistical significance using the log-rank test. Multivariate Cox regression analysis was used to examine the associations between treatment outcome and various prognostic factors, and between FDG uptake and tumor-related factors. $P < 0.1$ was used as the criterion for inclusion in the multivariate model. All statistical tests were two-sided, and a $P < 0.05$ was considered significant. The diagnostic utility of independent predictors of extrahepatic metastasis recurrence was evaluated according to the area under the receiver operating characteristic curve (AUROC), sensitivity, specificity, positive predictive value, negative predictive value, and accuracy. The AUROC was classified as low (0.50–0.70), moderate (0.70–0.90), or high (0.90–1.0) accuracy. All statistical analyses were performed using IBM SPSS Statistics ver. 22 (IBM SPSS, Inc.).

Results

Patient characteristics

The baseline characteristics of the 67 patients included in this study are shown in Table 1. The patients comprised 55 males (mean age 67 range 33-84) and 12 females (mean age 67 range 37-82). Of the 67 patients, 19 (28.4%) were positive for hepatitis B surface antigen, 24 (35.8%) were positive for hepatitis C virus antibody, and 24 (35.8%) were negative for both hepatitis markers. Eleven patients (16.4%) had liver cirrhosis. The median tumor marker levels were 10.1 ng/mL (range, 1.0–290700 ng/mL) for AFP, 3.2% (range, < 0.5–78.4%) for lens culinaris agglutinin A-reactive fraction of AFP (AFP-L3), and 82 mAU/mL (range, 10–430910 mAU/mL) for des-γ-carboxyprothrombin (DCP). Of the 67 patients, 48 (71.6%)

underwent anatomic resection and 19 (28.4%) partial resection. A single tumor nodule was present in 46 patients (68.7%) and multiple nodules in 21 patients (31.3%). The mean tumor size was 41.0 ± 35.6 mm (range, 8.0–200 mm).

The pathological findings are shown in Table 1. For patients with multiple tumors, the largest tumor lesion was used for the statistical analyses. Among the 67 main nodules from the resected specimens, 27 (40.3%) and 40 (59.7%) were classified as SN and non-SN type HCC, respectively, and 2 (3.0%), 46 (68.7%), and 19 (28.4%) were classified as well, moderately, and poorly differentiated, respectively. Extrahepatic metastasis recurrence was observed in 12 cases (17.9%), 11 of which occurred within 2 years. The sites of metastasis were the lung (n = 8), lymph nodes (n = 3), bone (n = 3), perineum (n = 1), and skin (n = 1) (there were overlapping cases).

Prediction of distant metastasis recurrence

A cutoff TNR of 1.53 was determined according to the maximum sum of the sensitivity and specificity. Significant predictors of distant metastasis recurrence identified by the univariate analyses included an AFP level > 100 ng/ml, AFP-L3 level > 10 %, DCP level > 100 mAU/ml, maximum tumor size ≥ 50 mm, macroscopic type non-SN, tumor cell poor differentiation, and TNR ≥ 1.53. Multivariate logistic regression analysis identified a TNR ≥ 1.53 (hazard ratio [HR], 0.037; P = 0.003), multiple tumor nodules (HR, 0.121; P = 0.007), and presence of MVI (HR, 0.094; P = 0.003) as independent predictors of extrahepatic metastasis recurrence (table 2). The diagnostic abilities of these factors are shown in Figure 3 and Table 3. The AUROC for predicting extrahepatic metastasis recurrence were 0.869 for TNR, 0.748 for multiple tumor nodules and 0.705 for presence of MVI. A TNR ≥ 1.53 exhibited a sensitivity of 91.7%, specificity of 76.4%, positive predictive value of 45.8%, negative predictive value of 97.7%, and accuracy of 79.1%. The cumulative rates of

extrahepatic metastasis recurrence are shown in Figure 4. The recurrence rate was 16.4% after both 1 and 2 years. A TNR ≥ 1.53, multiple tumor nodules, and presence of MVI were each associated with a significantly higher recurrence rate, compared with a TNR < 1.53, single tumor nodule, and absence of MVI, respectively.

Factors associated with a TNR ≥ 1.53 in HCC according to univariate and multivariate analyses

The factors identified as having an association with a TNR ≥ 1.53 are shown in Table 4. In the univariate analysis, AFP level > 100 ng/ml, AFP-L3 level > 10 %, DCP level > 100 mAU/ml, maximum tumor size ≥ 50 mm, macroscopic type non-SN, tumor cell poor differentiation, and presense of MVI were identified as significant factors. In the binomial logistic regression, poor tumor cell differentiation (OR, 0.24; P = 0.044) and tumor size >50mm (OR, 1.043; P = 0.002) remained significant.

Discussion

This study examined the ability of preoperative ^{18}F FDG PET-CT to predict the recurrence of extrahepatic metastasis. The rate of extrahepatic metastasis recurrence after 1 year is 16.4% (11/67) in total (Figure 4), and it is impressed that it is high. In this study, many cases (31.3% (21/67)) exceeding the Milan criteria were contained, so there was a possibility that rate of extrahepatic metastasis recurrence was high. If the risk of extrahepatic metastasis recurrence can be evaluated preoperatively, it may provide a useful criterion for determining adjuvant therapy [7,8,9] and surgical procedure decisions.

Multivariate analysis was performed to identify predictors of extrahepatic metastasis recurrence. As a result, a TNR ≥ 1.53, multiple tumor nodules, and the presence of MVI were significant independent factors (Table 2). The abilities of these three factors to diagnose the

recurrence of extrahepatic metastasis are shown in Table 3. The sensitivity, specificity, and accuracy were 45.5%, 91.0%, and 83.3%, respectively, for MVI and 66.7%, 76.4%, and 74.6%, respectively, for multiple nodules. Both parameters exhibited good accuracies, but this may be a reflection of their high specificities and the low prevalence, the low sensitivities are problematic for detecting high-risk lesions. In addition, since MVI is a postoperative pathological finding, it cannot be used as a criterion for determining the treatment policy preoperatively.

The AUROC for the TNR was 0.869, and the diagnostic ability of a TNR ≥ 1.53 showed excellent sensitivity (91.7%) and good specificity (76.4%) and accuracy (79.1%). Recently, reports have shown that PET can detect the presence of MVI, degree of tumor differentiation, as well as other parameters in HCC [12,13,14,15,16].

HCC is reported to have poor FDG uptake because of low GLUT1, low hexokinase 2 (HK2) and high G6Pase expression. ^{18}F-FDG is transported into cells by GLUT1, where it is then phosphorylated by HK2 to afford charged ^{18}F-FDG-6-phosphate that accumulates within the cell. G6Pase can hydrolyze ^{18}F-FDG-6-phosphate to ^{18}F-FDG that may then be transported back out of cancer cells.

It is reported that higher FDG uptake, higher GLUT1 expression and lower G6Pase expression are greater in poorly differentiated HCC than moderately differentiated HCC [11, 20].

Among the 12 cases in which extrahepatic metastasis recurred, 1 had a TNR < 1.53. This case was characterized by an HCC etiology of HBV infection, main tumor size of 50 mm, single lesion, AFP level of 7.7 ng/mL, AFP-L3 level of 6.2%, DCP level of 29 mAU/mL, and TNR of 1.4. Anatomical resection was performed, and the pathological findings indicated poor tumor differentiation, a single nodule (not multiple), and absence of MVI, and multiple bone

metastases developed at 11 months after the operation. Among the preoperative tumor factors evaluated in this study, only the main tumor size was a significant diagnostic factor for recurrence of extrahepatic metastasis. Among the PET-CT findings, the TNR (1.4) and tumor SUVmax (3.75) were higher than general value, but they were lower than our set cutoff value. Conversely, there was a case in which only the TNR, among the preoperative tumor factors evaluated, suggested the possibility of extrahepatic metastasis recurrence. This case was characterized by an HCC etiology of HBV infection, main tumor size of 30 mm, single lesion, AFP level of 7.5 ng/mL, AFP-L3 level of < 0.5%, DCP level of 30 mAU/mL, and TNR of 2.67. Anatomical resection was performed, and the pathological findings indicated poor tumor differentiation, a single nodule, and presence of MVI, and lymph nodule metastasis was observed 2 months after the operation.

In the binomial logistic analysis, poor differentiation and large tumor size were significant factors associated with a TNR ≥ 1.53 (Table 4) and thus may be closely involved in FDG uptake. However, in the univariate analyses, most of the other factors evaluated also showed significant associations, and the possibility that these other factors are involved cannot be ruled out. To understand the exact implications of FDG uptake in HCC, molecular studies are necessary.

The present study has several limitations. First, the possibility of selection bias cannot be excluded because of the study's retrospective nature. Second, our sample size is relatively small and was drawn from a single facility.

In conclusion, PET-CT findings and MVI are useful predictors of extrahepatic metastasis recurrence after surgery. Since PET-CT can be used to acquire tumor information non-invasively before treatment, it is useful for deciding the future treatment course.

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Figure legends

Fig. 1a. This is a 30 mm single HCC case of liver S6. Preoperative PET-CT showed strong uptake of FDG, suggesting a low degree of differentiation. **Fig. 1b.** Three months after resection, metastases occurred in the para-aortic, supraclavicular, and mediastinal lymph nodes.

Fig. 2. Flow chart of slection processes of patients in the present study

Fig. 3. Receiver operating characteristic curves demonstrating the abilities of the tumor-to-normal liver standardized uptake value ratio (TNR), number of tumor nodules (single vs. multiple), and microvascular invasion (MVI; presence vs. absence) to predict recurrence of extrahepatic metastasis. The areas under the receiver operating characteristic curve (AUROCs) of these factors were 0.869, 0.748, and 0.705, respectively.

Fig. 4. Cumulative rates of extrahepatic metastasis recurrence after HCC resection (a) The 1- and 2-year recurrence rates for all patients. Comparisons of the recurrence rates according to (b) the tumor-to-normal liver standardized uptake value ratio (TNR; ≥ vs. < 1.53), (c) microvascular invasion (MVI; presence vs. absence), and (d) number of tumor nodules (single vs. multiple).

Table legends

Table 1. Characteristics of the 67 patients

Table 2. Univariate and multivariate analyses of diagnostic factors for extrahepatic metastasis recurrence

Table 3. Diagnostic abilities of a TNR ≥ 1.53, multiple nodules, and MVI for extrahepatic metastasis recurrence

Table 4. Univariate and multivariate analyses of factors associated with a TNR ≥ 1.53

Figure 1(a)

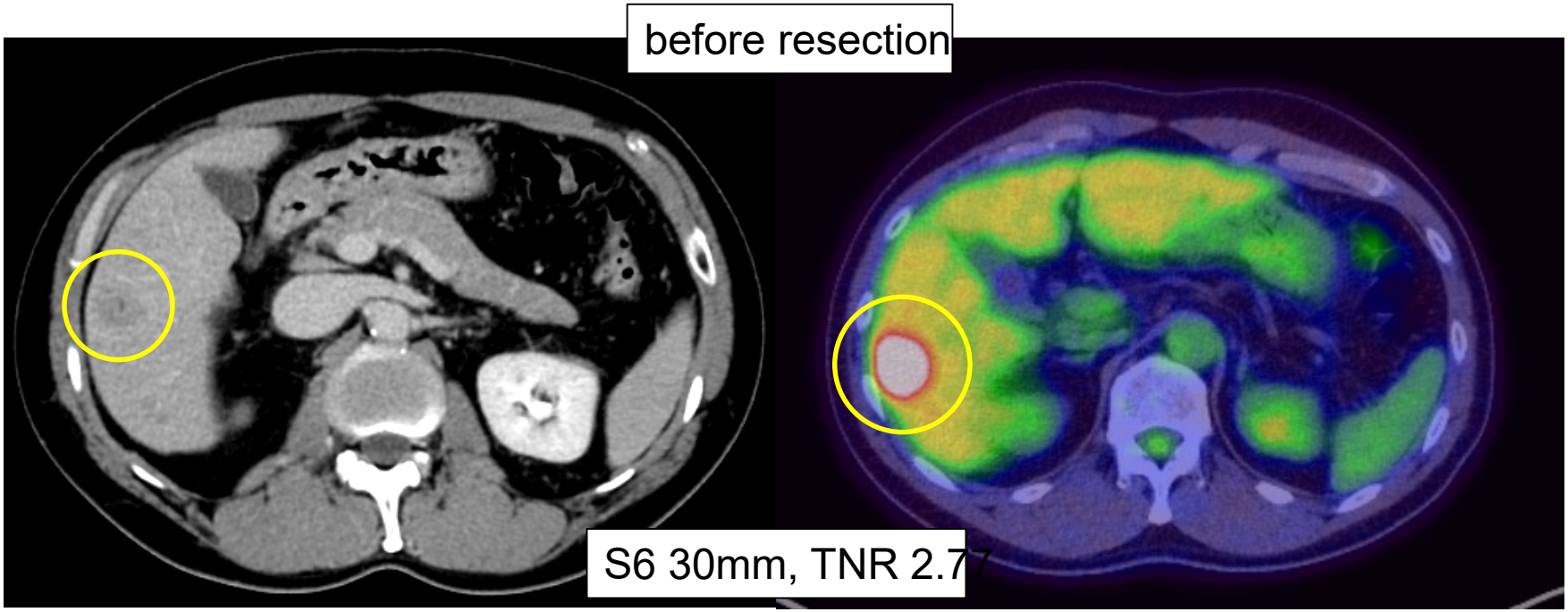

Figure 1(b)

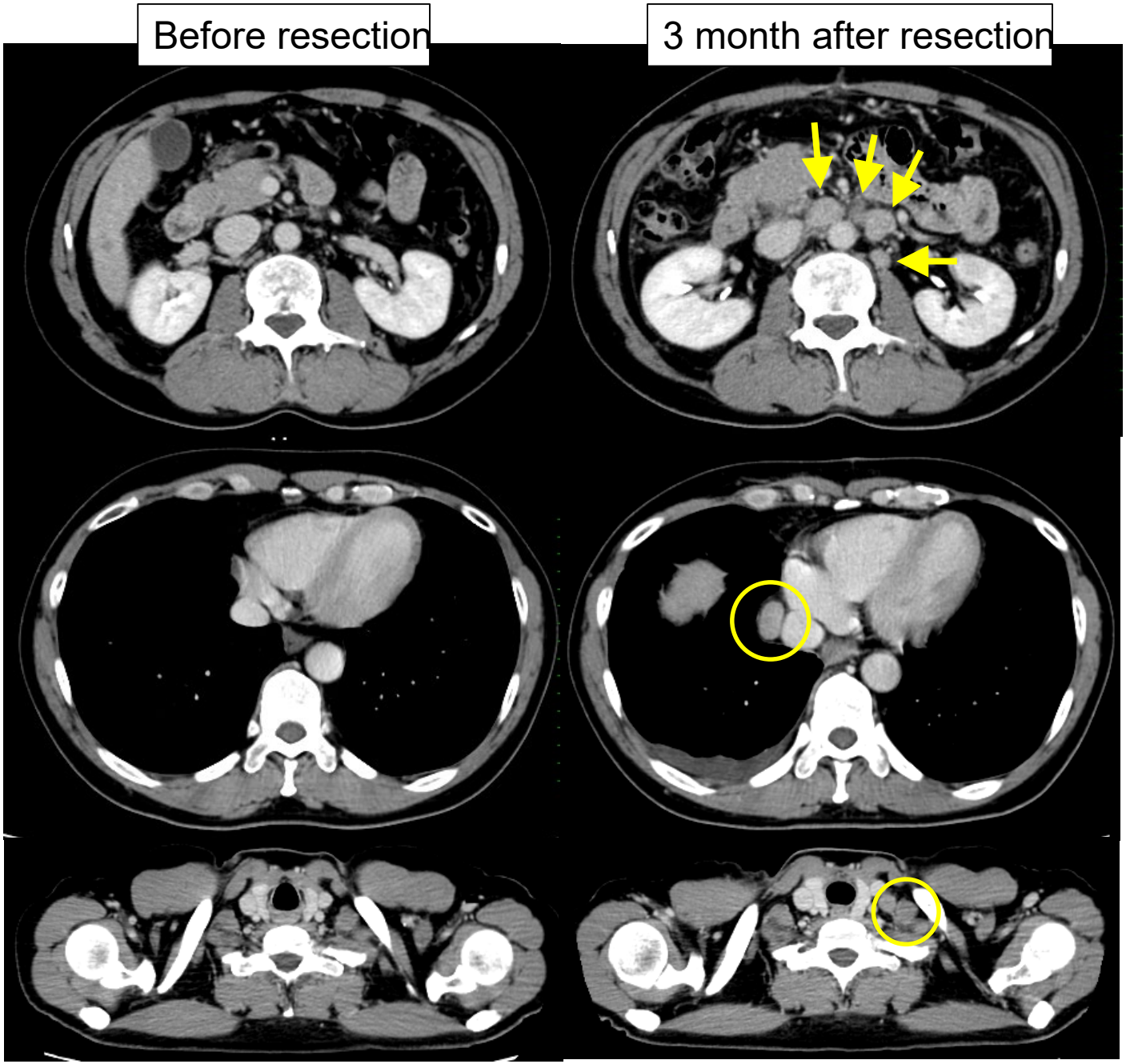

Figure 2

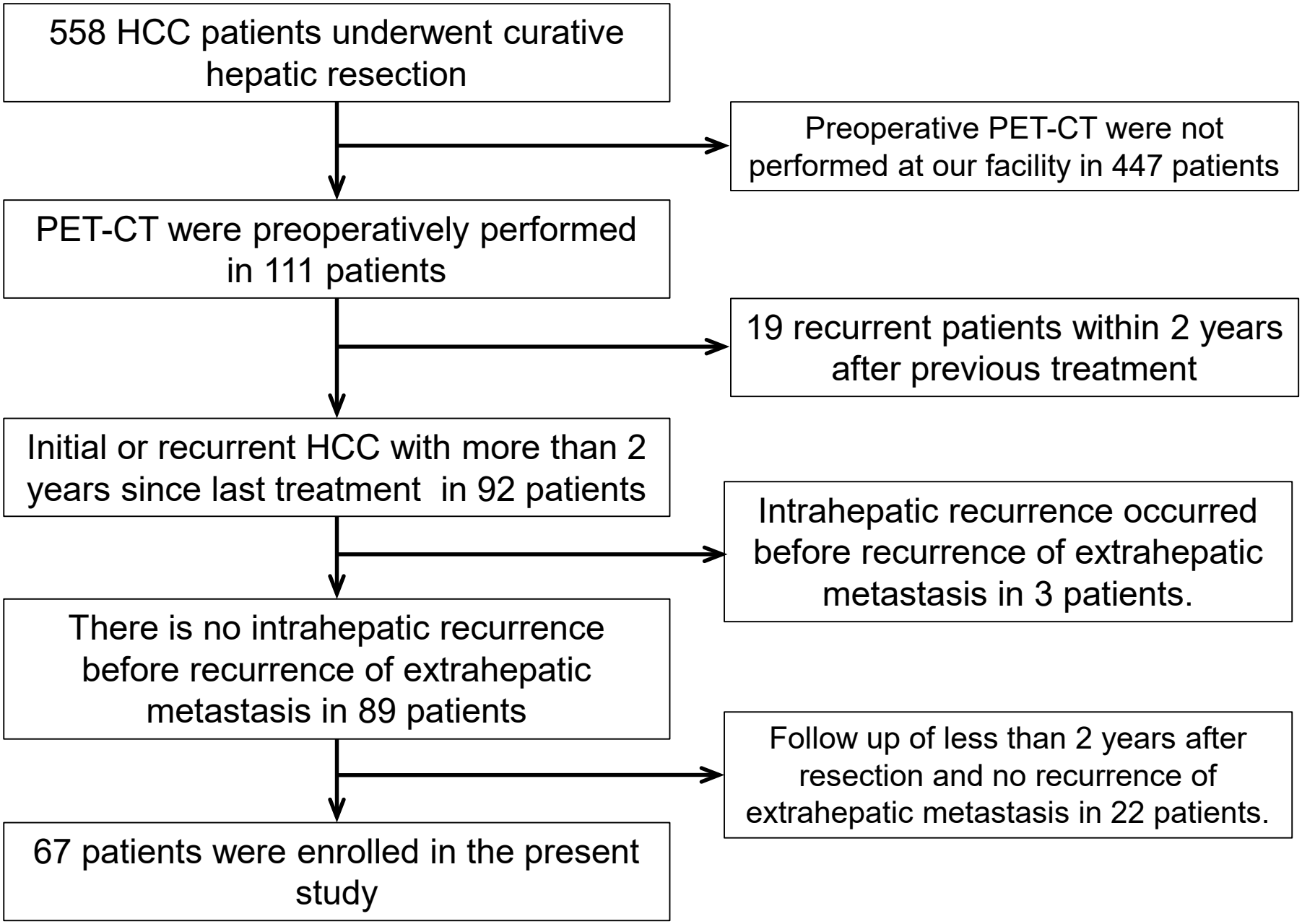
558 HCC patients underwent curative hepatic resection
Preoperative PET-CT were not performed at our facility in 447 patients
PET-CT were preoperatively performed in 111 patients
19 recurrent patients within 2 years after previous treatment
Initial or recurrent HCC with more than 2 years since last treatment in 92 patients
Intrahepatic recurrence occurred before recurrence of extrahepatic metastasis in 3 patients.
There is no intrahepatic recurrence before recurrence of extrahepatic metastasis in 89 patients
Follow up of less than 2 years after resection and no recurrence of extrahepatic metastasis in 22 patients.
67 patients were enrolled in the present study

Figure 3

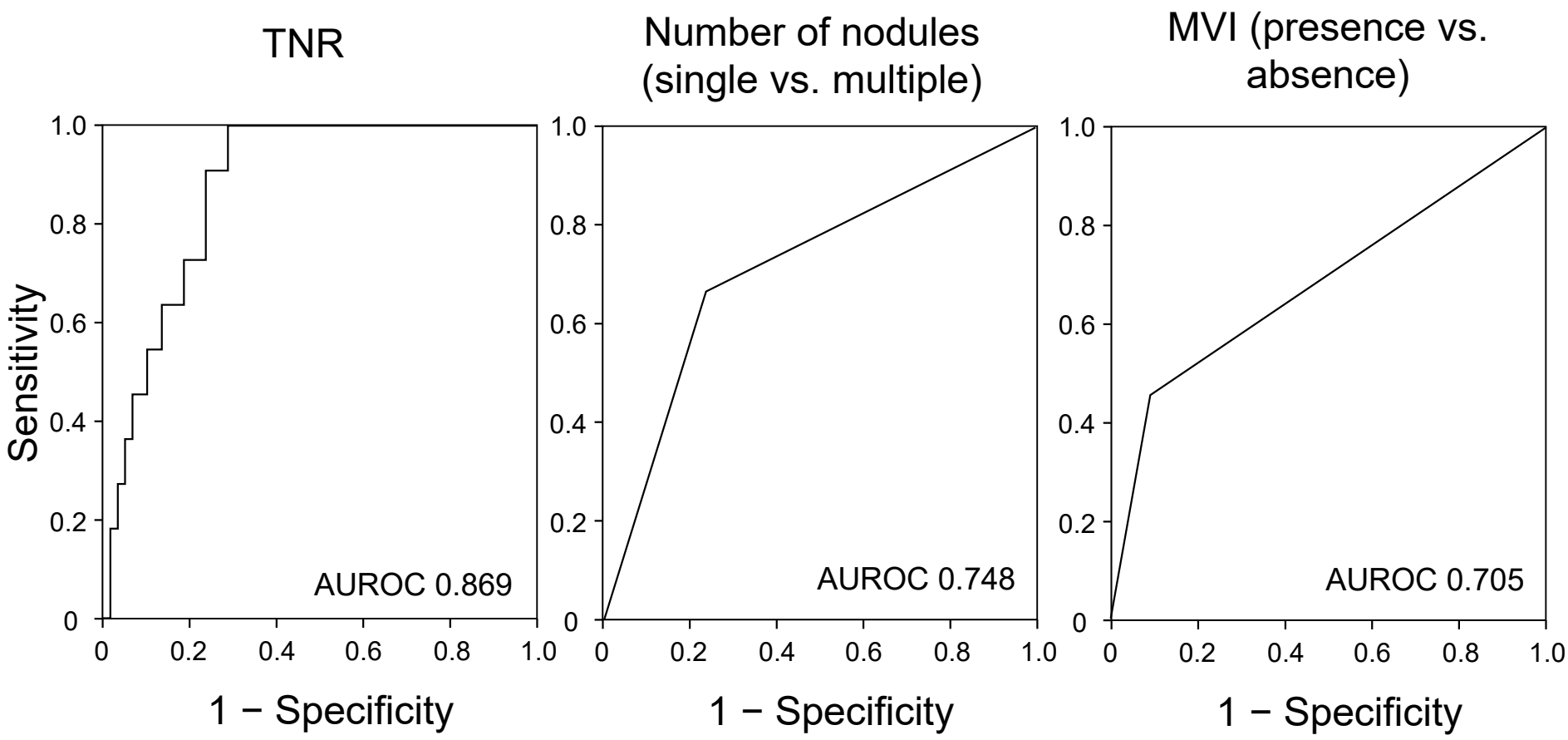
TNR
Number of nodules (single vs. multiple)
MVI (presence vs. absence)
Sensitivity
1 − Specificity
1 − Specificity
1 − Specificity
AUROC 0.869
AUROC 0.748
AUROC 0.705
0
0.2
0.4
0.6
0.8
1.0

Figure 4

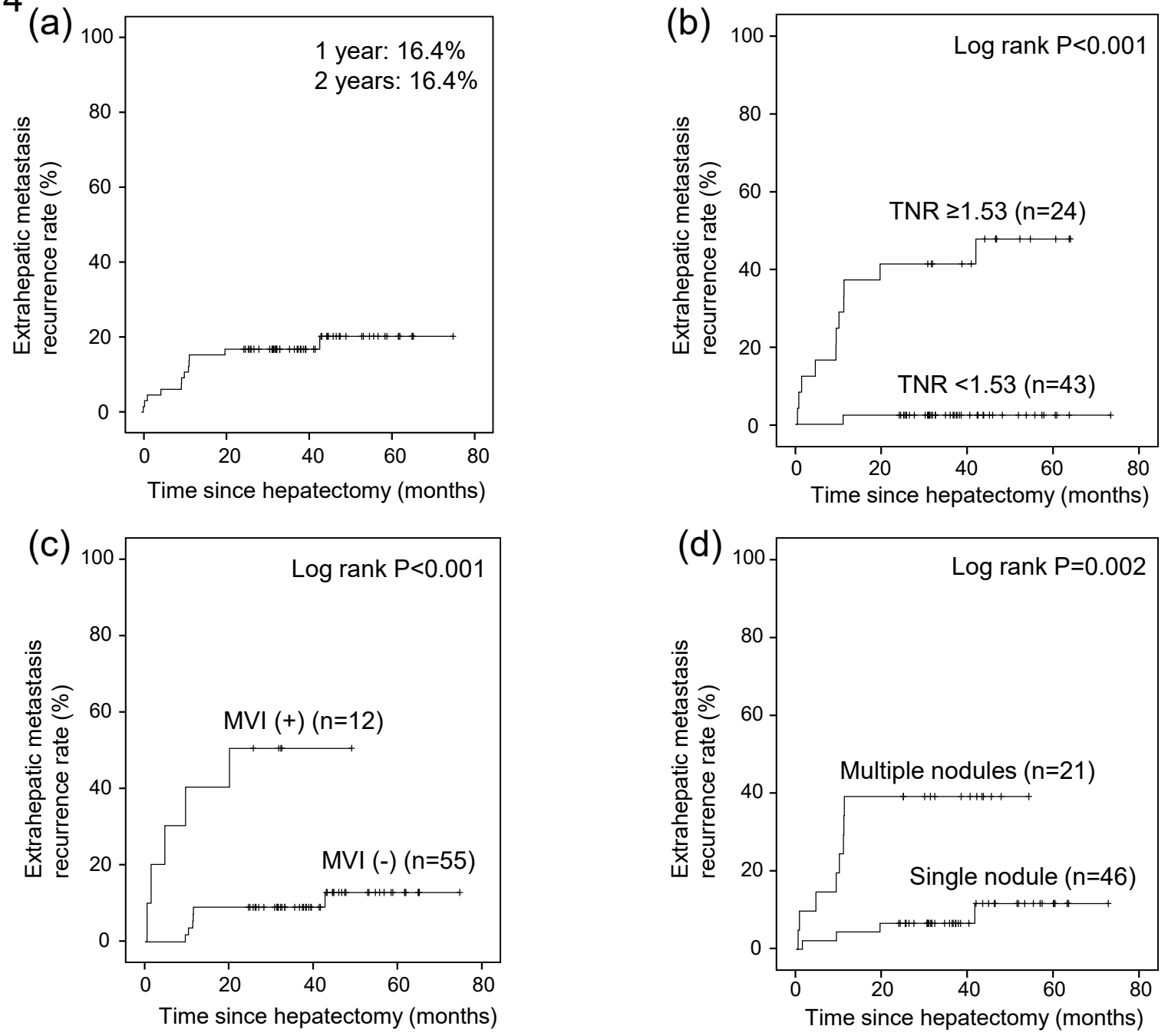
(a)
1 year: 16.4%
2 years: 16.4%
Extrahepatic metastasis recurrence rate (%)
Time since hepatectomy (months)
(b)
Log rank P<0.001
TNR ≥1.53 (n=24)
TNR <1.53 (n=43)
Extrahepatic metastasis recurrence rate (%)
Time since hepatectomy (months)
(c)
Log rank P<0.001
MVI (+) (n=12)
MVI (-) (n=55)
Extrahepatic metastasis recurrence rate (%)
Time since hepatectomy (months)
(d)
Log rank P=0.002
Multiple nodules (n=21)
Single nodule (n=46)
Extrahepatic metastasis recurrence rate (%)
Time since hepatectomy (months)

Figure 5

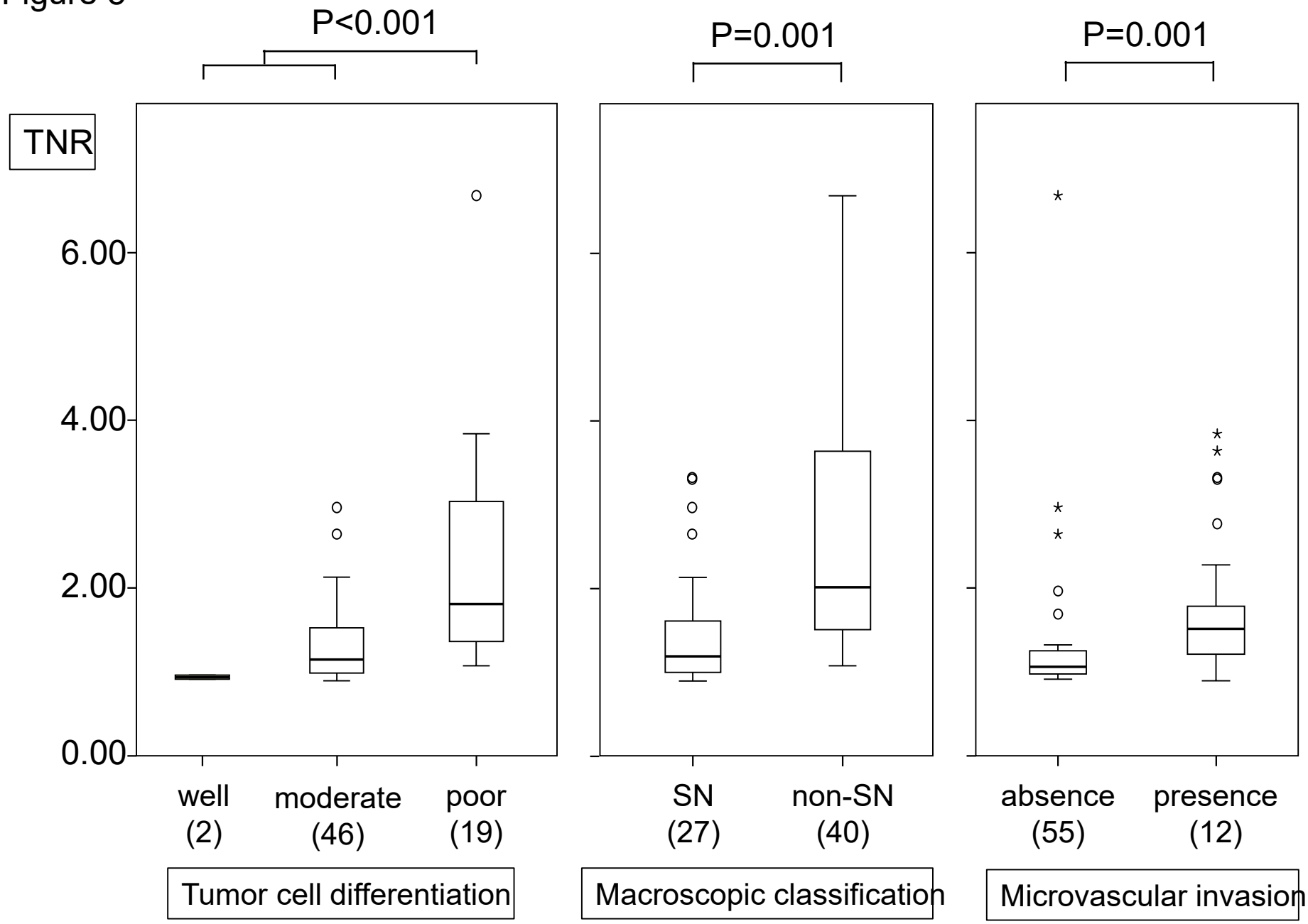
P<0.001
P=0.001
P=0.001
TNR
6.00
4.00
2.00
0.00
well
(2)
moderate
(46)
poor
(19)
SN
(27)
non-SN
(40)
absence
(55)
presence
(12)
Tumor cell differentiation
Macroscopic classification
Microvascular invasion

Table 1. Characteristics of the 67 patients

Variable	n = 67
Age, years*	68 (34–85)
Sex (male / female)	55 / 12
Etiology (HBV / HCV / NBNC)	19 / 24 / 24
Chronic hepatitis / liver cirrhosis	56 / 11
AFP, ng/mL*	10.1 (1.0–290700)
AFP-L3, %*	3.2 (<0.5–78.4)
DCP, mAU/mL*	82 (10–430910)
Number of tumor nodules (single / multiple)	46 / 21
Maximum tumor size, mm**	41.0 ± 35.6
Macrovascular invasion (- / +)	63 / 4
18F-FDG PET-CT TNR*	1.59 (0.89–6.68)
Postoperative adjuvant therapy (- / +)	52 / 15
Anatomical resection / partial resection	48 / 19
Pathological finding	
Macroscopic classification (SN / non-SN)	27 / 40
Tumor cell differentiation (well / moderate / poor)	2 / 46 / 19
Microvascular invasion (absence / presence)	55 / 12
Vp (- / +)	58 / 9
Vv (- / +)	64 / 3
Va (- / +)	65 / 2

* Median (range)
** Mean ± SD
HBV, hepatitis B virus; HCV, hepatitis C virus; NBNC, patients negative for both HBs antigen and HCV antibody; AFP, α-fetoprotein; AFP-L3, lens culinaris agglutinin a-reactive α-fetoprotein; DCP, des-γ-carboxyprothrombin; ^{18}F-FDG PET-CT, fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography; TNR, tumor-to-normal liver standardized uptake value ratio; SN, simple nodular; non-SN, non-simple nodular

Table 2. Univariate and multivariate analyses of diagnostic factors for extrahepatic metastasis recurrence

Variable	P	Hazard ratio	95% CI	p
AFP ≥100/<100 ng/mL	0.061	0.810	0.123-5.354	0.28
AFP-L3 ≥10/<10%	0.008	1.573	0.226-10.953	0.557
DCP ≥100/<100 mAU/mL	0.006	3.239	0.180-58.297	0.403
Number of tumor nodules (single/multiple)	0.002	0.121	0.026–0.559	0.007
Maximum tumor size ≥50/<50 mm	<0.001	1.015	0.992-1.038	0.288
18F-FDG PET-CT TNR ≥1.53/<1.53	<0.001	0.037	0.004–0.337	0.003
Anatomical resection/partial resection	0.492	0.215	0.021-2.218	0.197
Macroscopic classification (SN/non-SN)	0.003	0.003	0.001-1.247	0.067
Tumor cell differentiation (moderate or well/poor)	<0.001	0.544	0.055-5.384	0.117
Microvascular invasion (absent/present)	<0.001	0.094	0.020–0.440	0.003

CI, confidence interval; AFP, α-fetoprotein; AFP-L3, lens culinaris agglutinin a-reactive α-fetoprotein; SN, simple nodular; non-SN, non-simple nodular; 18F-FDG PET-CT, fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography; TNR, tumor-to-normal liver standardized uptake value ratio

Table 3. Diagnostic abilities of a TNR ≥ 1.53, multiple nodules, and MVI for extrahepatic metastasis recurrence

	TNR ≥ 1.53	Multiple nodules	MVI presence
Sensitivity, %	91.7	66.7	45.5
Specificity, %	76.4	76.4	91
Positive predictive value, %	45.8	38.1	50
Negative predictive value, %	97.7	91.3	89.3
Accuracy, %	79.1	74.6	83.3

TNR, tumor-to-normal liver standardized uptake value ratio; MVI, microvascular invasion

Table 4. Univariate and multivariate analyses of factors associated with a TNR ≥ 1.53

Variable	TNR < 1.53 (n = 43)	TNR ≥ 1.53 (n = 24)	P	Odds ratio	95% CI	P
AFP, ng/mL*	7.0 (1.0–2330)	92.6 (1.3-290700)	0.03			0.597
AFP-L3, %*	1.3 (<0.5–66.6)	17.4 (<0.5–78.4)	0.014			0.394
DCP, mAU/mL*	34 (10–17860)	2260 (15–430910)	<0.001			0.303
Number of tumor nodules (single / multiple)	33 / 10	13 / 11	0.056			0.444
Maximum tumor size, mm**	26.8 ± 29.3	67.0 ± 33.8	<0.001	1.043	1.015–1.071	0.002
Macroscopic classification (SN / non-SN)	22 / 21	5 / 19	0.015			0.39
Tumor differentiation (well or moderate / poor)	37 / 6	11 / 13	<0.001	0.24	0.060–0.962	0.044
Microvascular invasion (absence / presence)	40 / 3	14 / 9	0.017			0.667

*Median (range)

** Mean ± SD

CI, confidence interval; SN, simple nodular; non-SN, non-simple nodular; TNR, tumor-to-normal liver standardized uptake value ratio; AFP, α-fetoprotein; AFP-L3, lens culinaris agglutinin a-reactive α-fetoprotein; DCP, des-γ-carboxyprothrombin