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Conflict of interest

The authors declare that they have no conflict of interest.

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Abstract

Background and Aim: The natural course and clinical implications of hypovascular lesions on dynamic CT and/or Gd-EOB-DTPA-enhanced MRI (EOB-MRI) were investigated.

Methods: We followed the patients with hepatocellular carcinoma (HCC) who underwent hepatectomy between April 2009 and August 2012 to determine whether new classical HCCs developed from these unresected borderline lesions or emerged in different areas

Results: One hundred and eleven patients with hepatocellular carcinoma (HCC) were identified to have undergone examinations using both imaging modalities before hepatic resection. A total of 54 hypovascular lesions were detected. EOB-MRI detected 51 lesions, while dynamic CT identified 21 lesions. Eleven lesions were resected at the time of the hepatectomy together with the main HCCs. Classical HCCs had developed from 52.5% of the 43 unresected lesions at 3 years after hepatic resection. Subsequently, we conducted a patient-by-patient analysis to compare the development of classical HCC from these hypovascular lesions and the emergence of de novo classical HCC in other areas. The 3-year occurrence rate was 62.2% for the former group and 55.0% for the latter group ($P = 0.83$). Thus, although 52.2% of these hypovascular lesions had developed into classical HCCs at 3 years after the initial hepatectomy, de novo HCCs also occurred at other sites. Furthermore, new hypovascular lesions emerged after hepatectomy in 18-29 % of patients irrespective of the presence or absence of hypovascular lesions at hepatectomy.

Conclusions: It remains uncertain whether these hypovascular lesions should be resected together with the main tumors at the time of hepatectomy.

Key words

Liver surgery

Hepatocellular carcinoma, clinical

Liver imaging

EOB MRI

Hypovascular lesion

Introduction

Hepatocellular carcinoma (HCC) is one of the most prevalent types of cancer, particularly in southern and eastern Asia. It is the sixth most common cancer in the world and the third most common cause of cancer-related death.[1] In Japan, HCC is the third most common cause of cancer-related death among men and the fifth most common among women.[2]

The mainstay of treatment for HCC is hepatic resection; however, a high frequency of postoperative intrahepatic recurrence has been reported, the majority of which are thought to be metachronous multicentric recurrences.[3] HCC is known to follow a stepwise development from a low-grade dysplastic nodule to a high-grade dysplastic nodule, and finally to typical HCC.[4] On multidetector helical dynamic computed tomography (CT), typical HCCs show early hypervascularization and delayed hypoattenuation. On the other hand, borderline lesions are usually hypovascular and lack arterial enhancement. Recently, the detection of these borderline lesions has been reportedly increasing because of the development of gadolinium ethoxybenzyl diethylene triamine pentacetic acid-enhanced magnetic resonance imaging (EOB-MRI).[5,6] Accompanying borderline lesions have also been increasingly detected in preoperative imaging examinations for HCC. However, the natural course and clinical implications of these lesions remain largely unknown. Furthermore, a consensus has not been reached as to whether these lesions should be resected together with classical HCC at the time of hepatectomy, i.e., with the main lesions requiring resection.[7-11]

In the present study, we followed the natural course of these borderline lesions after a hepatectomy for the main lesions. Finally, we attempted to clarify the clinical implications of these lesions.

Materials and Methods

Subjects. The present study was approved by our Hospital Ethics Committee (authorization number 16-063). The institutional review board did not require informed consent for the use of the patients' medical records or imaging examinations.

The inclusion criteria were as follows: (a) patients who underwent a surgical resection for HCC at our institution between April 2009 and August 2012, (b) patients who underwent both EOB-MRI and multidetector helical dynamic CT imaging prior to surgery, and (c) patients who underwent follow-up studies involving multidetector helical dynamic CT and/or EOB-MRI after surgery.

Imaging techniques. The CT examinations were performed using an Aquilion One system using a 320-detector scanner and a slice thickness of 1 mm (Toshiba Medical Systems, Japan). The CT examinations were performed 30, 80 and 180 seconds after the start of the injection of nonionic contrast material at a dose of 2 mL/kg body weight (Omnipaque 300; DAIICHI SANKYO COMPANY, Japan). The MRI examinations were performed using a 1.5-Tesla whole-body MR system (EXCELART Vantage Powered by Atlas; Toshiba Medical Systems, Japan, or MAGNETOM Avanto 1.5 T; Siemens Healthineers Japan, Japan) with a 12-channel phased array receiver coil at a slice thickness of 2.5 mm.

Gadolium-ethoxybenzyl-diethylenetriamine penta-acetic acid (PRIMOVIST; Bayer Schering Pharma AG, Berlin, Germany) was used as a contrast medium. After the injection of PRIMOVIST at a dose of 0.1 mL/kg, dynamic MRI was repeated at 25 seconds (hepatic arterial phase), 71 seconds (portal venous phase), 118 seconds (equilibrium phase), and 20 minutes (hepatobiliary phase) after the peak aortic enhancement time, which was determined using a test injection.

Liver resection. Preoperative planning for liver resection was indicated for all the lesions that were diagnosed as HCC based on the presence of both early hypervascularization and delayed hypoattenuation on CT or hyperintensity during the arterial phase and hypointensity during the hepatobiliary phase on MRI. After laparotomy, intraoperative ultrasonography (IOUS) was performed to confirm the preoperatively detected HCCs, borderline lesions, and to search for other liver tumours not identified preoperatively. All the liver tumours diagnosed as classical HCC on IOUS were resected, as permitted by the estimation of the residual hepatic functional reserve. The indications for liver resection and the operative procedures were determined according to a decision tree based on the liver function as previously described.[12] As a rule, the borderline lesions were not resected, although resections were occasionally performed at the attending surgeon's discretion, such as when the borderline lesion was located close to the main tumor.

Postoperative evaluation. After discharge, serum tumor markers (alpha-fetoprotein and plasma des-gamma-carboxyprothrombin) and multidetector dynamic CT and/or EOB-MRI findings were evaluated every 3-4 months. Recurrence was defined as the appearance of a new lesion with radiologic features typical of HCC or when the unresected liver lesions began to show a typical pattern of HCC or signs of enlargement during the postoperative period.

Two patient-based endpoints were set. Endpoint 1 was the time at which a classical HCC was found to have developed from the hypovascular lesions. We set this endpoint to investigate the clinical implications of hypovascular lesions. Endpoint 2 was the time at which a de novo classical HCC developed at a site other than an area corresponding to a hypovascular lesion.

Statistical analysis. A statistical analysis was performed using JMP computer software (SAS institute, Cary, NC, USA). Based on a lesion-by-lesion analysis, the cumulative risk of a hypovascular lesion developing into a classical HCC was calculated according to the Kaplan-Meier method. We calculated the hazard ratios according to size using a Cox proportional hazard regression.

For the patient-by-patient analysis, recurrence curves were constructed according to the Kaplan-Meier method using the two above-mentioned endpoints, and the log rank was used for statistical comparison. Values of $P < 0.05$ were considered to denote a statistically significant difference.

The difference in the sensitivities of EOB-MRI and dynamic CT for the detection of hypovascular lesions was estimated using the adjusted McNemar test to calculate the 95% confidence intervals (significance level was 5%).

Results

Patient characteristics

We identified 111 patients who met the inclusion criteria of the present study (Figure 1). The main characteristics of the patients are shown in Table 1 dividing them into those with hypovascular lesions (n=36) and without hypovascular lesions (n=75). None of baseline characteristics were different between the subgroups. Out of 111 patients, a total of 54 hypovascular lesions in the portal phase of dynamic CT or the hepatobiliary phase of EOB-MRI were detected in 36 patients (Fig. 2). The hepatobiliary phase of EOB-MRI revealed 52 hypovascular lesions in 34 patients, while the portal phase of dynamic CT revealed 20 hypovascular lesions in 9 patients. As shown in Figure 2, out of the 20 lesions detected using multidetector helical dynamic CT, 18 were also identified using EOB-MRI. On the other hand, out of 52 lesions detected using EOB-MRI, only 18 were identified using multidetector helical dynamic CT. Eleven hypovascular lesions were resected at the time of hepatectomy. Their pathological results were as follows: well differentiated HCC in 3, moderately differentiated HCC in 5, liver cyst in 1, and necrotic HCC in 2. The remaining 43 hypovascular lesions were unresected, and they developed into classical HCC at rates of 16.8% and 52.5% at 1 and 3 years, respectively (lesion-by-lesion analysis).

Development of classical HCC from hypovascular lesions detected by EOB-MRI and/or dynamic CT

First, we compared the development of classical HCC from 34 unresected lesions that were only identified using EOB-MRI and from nine unresected lesions that were detected using both dynamic CT and EOB-MRI (endpoint 1). The 1-year and 3-year rates of classical HCC occurrence were 14.3% and 49.3% with a median of 3.6 years for the former group and 25.0%

and 62.5% with a median of 2.1 years for the latter group, respectively (P = 0.29)(Fig. 3).

Development of classical HCC from hypovascular lesions stratified by the diameter

Next, we divided the 43 lesions into two groups according to their diameters, i.e., <10 mm and ≥10 mm, and compared the development of classical HCCs from these lesions. The cut-off size of 10 mm was set because this is the half size of the maximum diameter of early HCC (≤ 2cm) by the definition and also approximately the median size of the present 43 hypovascular lesions. The 1-year and 3-year rates of classical HCC occurrence were 17.7% and 26.8% with a median of 2.1years for the former group and 16.5% and 82.1% with a median of 1.4 years for the latter group. The difference was borderline significant (P = 0.053) (Fig. 4).

Development of classical HCCs from hypovascular lesions and the emergence of de novo classical HCCs in the other areas

Furthermore, we conducted a patient-by-patient analysis to compare the development of classical HCCs from hypovascular lesions identifiable using EOB-MRI and/or dynamic CT and the emergence of de novo classical HCCs in areas other than those corresponding to the hypovascular lesions (endpoints 1 and 2) in 26 patients whose borderline lesions had not been resected. The 1-year and 3-year occurrence rates were 26.8% and 62.2% with a median of 2.2 years for the former group and 28.3% and 55.0% with a median of 2.9 years for the latter group (P = 0.83) (Fig. 5).

Appearance of de novo classical HCCs from sites other than the borderline lesions after hepatectomy between patients with and without hypovascular lesions

Also, we compared the cumulative incidence of the appearance of de novo classical HCCs from sites other than the borderline lesions after hepatectomy between patients with (n = 36) and without (n = 75) hypovascular lesions identified during preoperative dynamic CT and/or EOB-MRI studies (endpoint 2, patient-by-patient analysis). The cumulative incidences at 1 year and 3 years were 32.8% and 67.1% with a median of 2.3 years for the former group and 19.9% and 43.4% with a median of 3.7 years for the latter group (P = 0.0968) (Fig. 6).

Overall incidence of the development of classical HCC in patients with and without hypovascular lesions

As described above, some residual hypovascular lesion developed to classical HCC and, in addition, de novo new HCC developed from other sites at a certain rate. We thus compared the overall incidence of the development of classical HCC during the follow-up period in patients with (n=36) and without (n= 75) hypovascular lesion at the time of hepatectomy. The cumulative incidences at 1 year and 3 years were 41.7% and 78.8% with a median of 1.6 years for the former group and 19.9% and 43.4% with a median of 3.7 years for the latter group (P = 0.0028) (Fig. 7).

New emergence of hypovascular lesions after hepatectomy

As expected, new hypovascular lesions may still develop during the follow-up period after hepatectomy. We compared the emergence of new hypovascular lesions after hepatectomy between patients with (n=36) and without (n=75) hypovascular lesions at the time of hepatectomy. The cumulative incidences at 1 year and 3 years were 14.3% and 27.5% with a median of 2.6 years for the former group and 4.8% and 18.1% with a median of 3.5 years for the latter group (P = 0.28) (Fig. 8)

Discussion

Gadolinium ethoxybenzyl diethlenetriamine pentaacetic acid (Gd-EOB-DTPA) is the most recently developed liver-specific contrast agent for use with MRI (EOB-MRI). Gd-EOB-DTPA works as both an extracellular and hepatocyte-specific contrast agent and provides both dynamic and hepatocyte-specific imaging.[13] Hypointense lesions during the hepatobiliary phase of EOB-MRI and hypoattenuating lesions during the portal phase of dynamic CT may appear to be similar, although their implications are completely different.[14]

Most hypoattenuating lesions visible during the portal phase of dynamic CT are detected as hypointense lesions (18/20) during the hepatobiliary phase of EOB -MRI. While only 35% (18/52) of the lesions that were detected as hypointense lesions in the hepatobiliary phase of EBO-MRI were detected using dynamic CT (Fig. 2). In the present study, two borderline lesions were only detected using dynamic CT. Both of these lesions were comparatively small in size (5 mm and 4 mm, respectively). The difference in the slice width between EOB-MRI and multidetector helical CT (2.5 mm vs. 1 mm) might have affected the difference in the detectability of these small lesions between EOB-MRI and multidetector helical CT.

Attenuation of hepatic nodules observed during the portal phase of dynamic CT usually indicates the decreased portal venous flow within the lesion. The reduced portal flow can be detected more clearly and at higher sensitivity by CT during arterial portography, although this imaging modality is considered to be an invasive method. With this modality, more hypovascular lesions that were idientified by EOB-MRI could be detected by CT.

In the present study, hypovascular lesions that were not resected at the time of hepatectomy developed into classical HCCs on imaging studies at 1-year and 3-year occurrence rates of 16.8% and 52.5%, respectively. Based on the present findings comparing EOB-MRI and multidetector helical dynamic CT as well as the observations of Kogita et al. , we hypothesized that hypovascular lesions that were only detectable using EOB-MRI represent an earlier stage of tumor in the multistep hepatocarcinogenesis process than those that were also identified using dynamic CT.[15] If this hypothesis is valid, the development rate of classical HCCs from lesions that were only detectable using EOB-MRI would likely be lower than that of lesions identified using both dynamic CT and EOB-MRI. We tested this hypothesis. Although the development rate of the former lesions tended to be lower than that of the latter lesions, a statistically significant difference was not observed, probably because of the small number of lesions included in the study (Fig. 3) Thus, this hypothesis remains to be tested in a larger study in the future.

Previous studies have reported the natural outcomes of hypoattenuated lesions on dynamic CT.[8,9,16] Takayasu et al. reported that hypoattenuated lesions in patients with chronic liver disease progressed to hypervascular lesions at frequencies of 15.8% and 58.7% at 1 and 3 years, respectively.[16] This result was similar to that of our study. A recent study examining EOB-MRI by Akai et al. reported that cumulative rates for hypointense lesions that became classical HCC were 3.2% at 1 year and 15.9% at 3 years, respectively.[8] Another EOB-MRI study by Kumada et al. reported that the overall 6-month and 12-month cumulative incidences of vascularization, i.e., the development of classical HCC, were 27.6% and 43.5%.[9] Therefore, compared with our result, Akai's study showed a lower incidence and Kumada's study demonstrated a higher incidence of vascularization. Likewise, the size of the lesions in Akais's study was smaller and that of Kumada's work was larger than that of our study. Thus, the size of lesions may affect the vascularization rate. We then tested this hypothesis by dividing the lesions into two groups depending on whether the lesion diameter was ≥10 mm or <10 mm. The larger lesions tended to develop into classical HCC more frequently than the smaller lesions ($P = 0.0532$) (Fig. 4). A similar result was reported by Kumada et al., who divided hypointense lesions observed using

EOB-MRI into those ≥15 mm and those <15 mm.[9]

In the patient-based analysis, the occurrence rate of de novo classical HCCs from sites different from those corresponding to hypovascular lesions were 28.3% and 55.0% at 1 and 3 years, respectively. These figures were almost comparable with the development of classical HCCs from borderline lesions (26.8% and 62.2% at 1 and 3 years) (Fig. 4). This finding suggests that although malignant transformation from borderline lesions occurred at a high rate, de novo HCC also emerged in areas different from these borderline lesions at a comparable rate after hepatectomy.

In addition, we found that patients with borderline lesions tended to develop de novo classical HCCs more frequently than patients without these lesions (Fig. 6). Consequently, overall incidence of the development of classical HCC, i.e., those from the hypovascular lesions and de novo new classical HCC, was significantly higher in patients with hypovascular lesions than those without these lesions (Fig 7). Furthermore, new hypovascular lesions emerged in 18-28 % of patients at 3 years after hepatectomy irrespective of the presence or absence of hypovascular lesions at the time of hepatecvtomy (Fig. 8). Based on these findings that new classical HCCs are likely to occur at a high frequency from sites other than those corresponding to the borderline lesions and the fact that the presence of borderline lesions themselves was a risk factor for the development of new classical HCC suggests that the aggressive treatment of these borderline lesions at the time of hepatectomy is not a straightforward decision. If the lesions are large (more than 10-15 mm), can also be detected using dynamic CT, and can be easily resected, such as those located near the surface of the liver, it might be worthwhile to resect these nodules at the time of hepatectomy.

It is surprising that eight of 11 hypovascular nodules that were resected together with main HCC were viable HCC pathologically. In particular, five of these lesions were already moderately differentiated HCC. These results were contradictory to what has been reported previously. However, it can not be concluded that these 11 nodules were representative of whole hypovascular lesions and conversely the possibility can not be denied that the lack of hypervascularity of these nodules might simply reflect the lower sensitivity to detect hypervascularity by noninvasive imaging modalities. The value of more sensitive but invasive methods to detect hypervascularity of HCC such as CT during hepatic arteriography might be re-evaluated.

The present study had some limitations. First, none of the lesions were histopathologically confirmed at the time of their diagnosis as a hypovascular lesion using EOB-MRI or dynamic CT, which is a limitation of this type of study. A histological diagnosis of biopsied hypovascular lesions may be difficult because of factors such as sampling errors for small lesions and intratumoral heterogeneity. Second, the number of cases and the number of lesions included in this study were relatively small. Indeed, the significance of in the differences in most comparisons was at borderline level. The lack of difference may be simply due to type II error. In contrast, the borderline difference observed may disappear with the increase in number of study patients. Future research utilizing a larger number of subjects is recommended to confirm and extend our results. Third, the imaging modality used for the follow-up of patients after hepatectomy was either dynamic CT or EOB-MRI in this retrospective study. A prospective study using a protocolled imaging study is needed to confirm the present results.

In conclusion, the ability of EOB-MRI to detect hypovascular lesions is superior to that of dynamic CT. The development of classical HCC from lesions identifiable solely by EOB-MRI tended to be lower than that from lesions detectable using both EOB-MRI and dynamic CT, although statistical significance was not reached. Although hypovascular lesions that can be identified by dynamic CT or EOB-MRI have some malignant potential and may develop into classical HCCs after hepatectomy, the occurrence of de novo HCCs from other sites was also frequent. The presence of these marginal lesions is considered to be a risk factor for recurrence in the remnant liver.

Table 1. Main characteristics of the 111 patients

Variable	With hypovascular lesions (n=36)	Without hypovascular lesions (n=75)	p-value
Age	69.6(38-81)	66.5 (36-86)	0.16†
Gender (males / females)	31/5	60/15	0.43‡
Hepatic virus status			0.33‡
HBV positive	13	24	
HCV positive	18	29	
HBV and HCV positive	0	1	
nonB nonC	5	21	
Number of HCCs at initial study			0.25†
Solitary	23	58	
2〜3	12	13	
4≤	1	4	
Size of primary HCCs (cm)	n=56	*n*=93	0.27†
1>	9	24	
1≤and 3>	26	27	
3≤	21	42	
Differentiation status of primary HCCs	n=56	n=93	0.89‡
Well	15	12	
Moderate	35	72	
Poor	6	9	
Vascular invasion status of primary HCCs	n=56	n=93	0.89‡
Vp0	46	79	
Vp1	8	10	
Vp2	0	1	
Vp3	1	2	
Vp4	1	1	
Level of serum bilirubin (mg/dL)	0.84 (0.3-1.45)	0.84 (0.34-1.75)	0.97†
1.0>	27	54	
1.0≤and 1.5>	9	20	
1.5≤	0	1	
ICG15 (%)	15.7 (5.2-29.3)	13.0 (1.1-47.6)	0.006§
10>	5	33	
10≤and 20>	21	31	

(Continues)

Table 1. (Continued)

Variable			
20≦and 30>	10	7	
30≦	0	4	
AFP (ng/dL)	16(1-7879)	6(1-12973)	0.29[§]
DCP (mAU/dL)	90.5(10-12251)	91(12-538100)	0.24[§]
Fibrosis			0.35[§]
0	1	9	
1	11	18	
2	5	14	
3	4	9	
4	15	25	
Activity			0.16[§]
0	7	26	
1	18	30	
2	10	19	
3	1	0	

†Student's t-test.

‡ Chi-squared test.

§ Mann-Whitney U test.

Data are median values or number of patients.

HBV, hepatitis B virus; HCV, hepatitis C virus; HCC, hepatocellular carcinoma; ICGR15, indocyanine green retention rate at 15 minutes; AFP, α-fetoprotein; DCP, des-gamma-carboxy pro-thrombin.

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Figure legends

Figure 1. Cohort selection criteria.

Figure 2. Venn diagram of hypovascular lesions identified using multidetector helical dynamic CT and/or EOB-MRI. EOB-MRI had a superior ability to detect hypovascular lesions, compared with dynamic CT ($P < 0.001$ McNemar test). The numbers in parentheses indicate those resected during the operation at the attending surgeon's discretion. A total of 11 lesions were resected.

Figure 3. Development of classical HCC from unresected lesions identifiable only using EOB-MRI (thick line, $n = 34$) and from unresected lesions detected using both EOB-MRI and dynamic CT (thin line, $n = 9$). Although the development rate of lesions identifiable using both EOB-MRI and dynamic CT was higher, no significant difference was observed ($P = 0.29$).

Figure 4. Development of classical HCC from borderline lesions according to the lesion diameter. The thin line indicates lesions <10 mm ($n = 23$), while the thick line denotes lesions ≥10 mm ($n = 20$). The difference was borderline significant ($P = 0.053$).

Figure 5. Patient-by-patient analysis ($n = 26$) investigating the occurrence of classical HCC from hypovascular lesions (thick line) and the occurrence of de novo classical HCC (thin line) in areas other than these lesions. No significant difference was observed ($P = 0.83$).

Figure 6. Cumulative distribution of the appearance of de novo HCC after a hepatectomy in

patients with (thick line, n = 36) and without (thin line, n = 75) hypovascular lesions preoperatively identified using dynamic CT and/or EOB-MRI. The difference was borderline significant (P = 0.0968).

Figure 7. Overall incidence of the development of classical HCC in patients with (n=36, thick line) and without (n=75, thin line) hypovascular lesions (P=0.0028). Overall incidence of classical HCC includes the development of classical HCC from the hypovascular lesion during the follow-up period after hepatectomy and de novo classical HCC.

Figure 8. New emergence of hypovascular lesions after hepatectomy in patients with (n=36, thick line) and without (n=75, thin line) hypovascular lesions at the time of hepatectomy (P=0.28)

Fig. 1

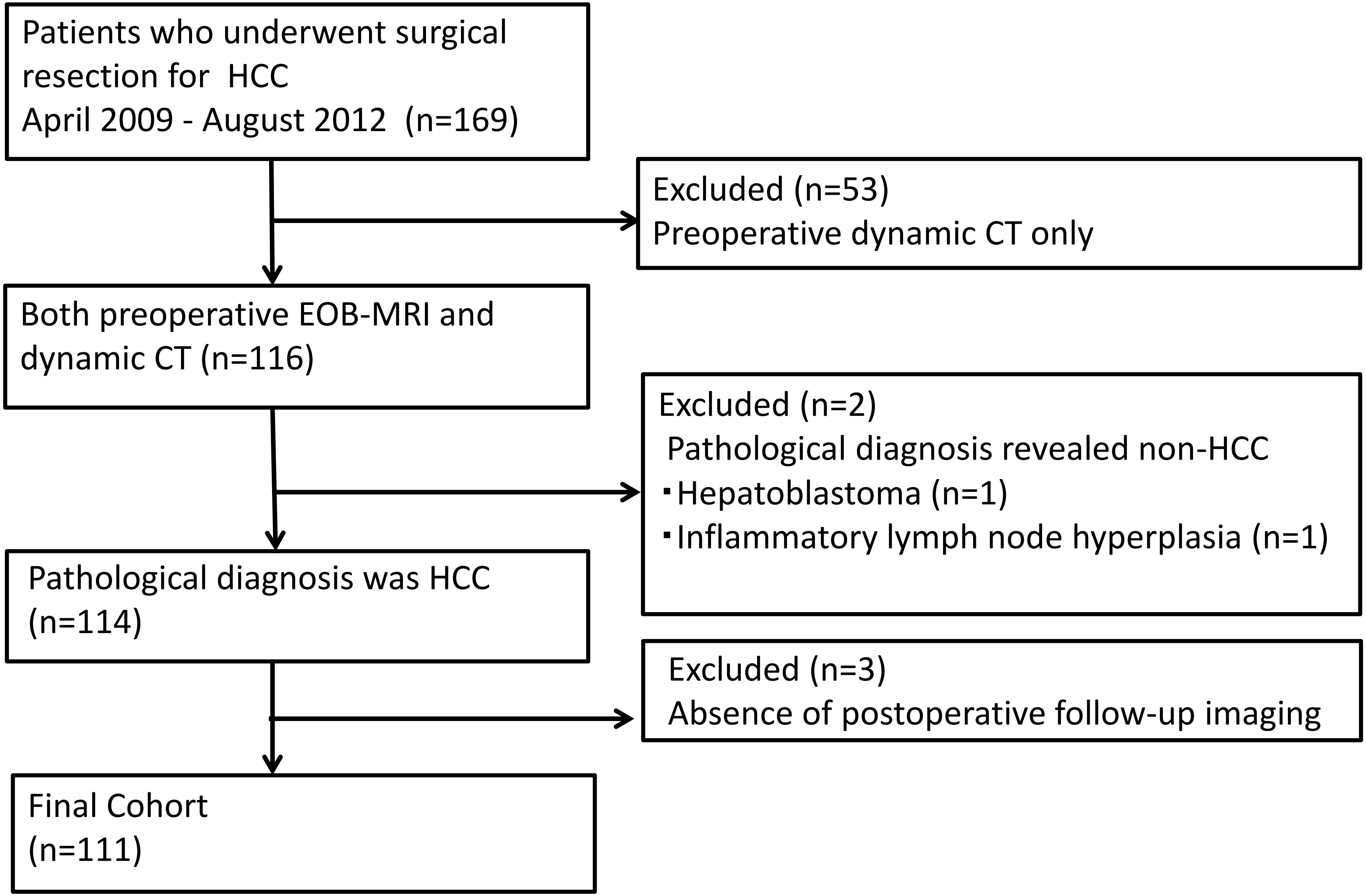

Patients who underwent surgical resection for HCC
April 2009 - August 2012 (n=169)
Excluded (n=53)
Preoperative dynamic CT only
Both preoperative EOB-MRI and dynamic CT (n=116)
Excluded (n=2)
Pathological diagnosis revealed non-HCC
▪Hepatoblastoma (n=1)
▪Inflammatory lymph node hyperplasia (n=1)
Pathological diagnosis was HCC (n=114)
Excluded (n=3)
Absence of postoperative follow-up imaging
Final Cohort (n=111)

Fig. 2

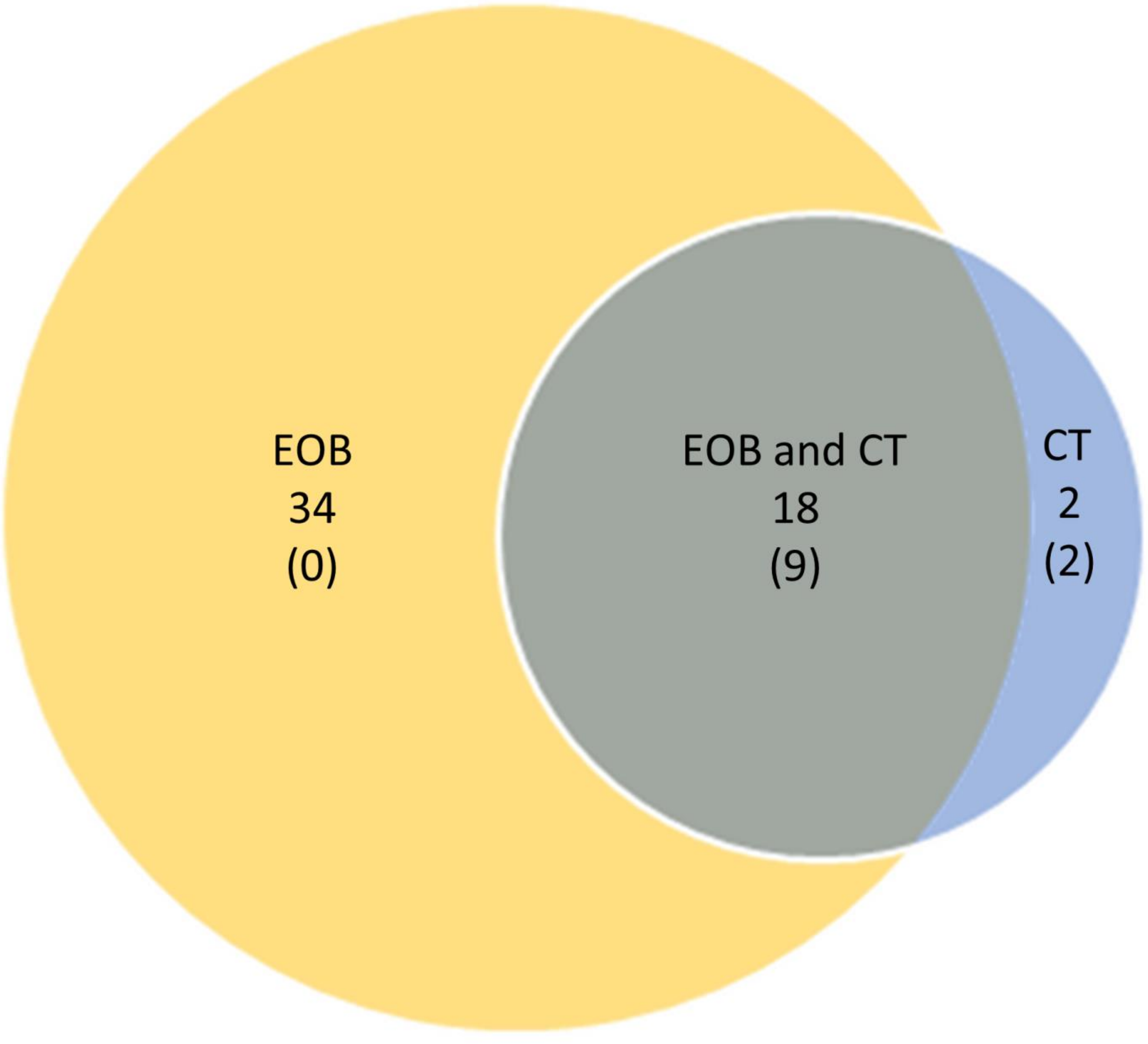
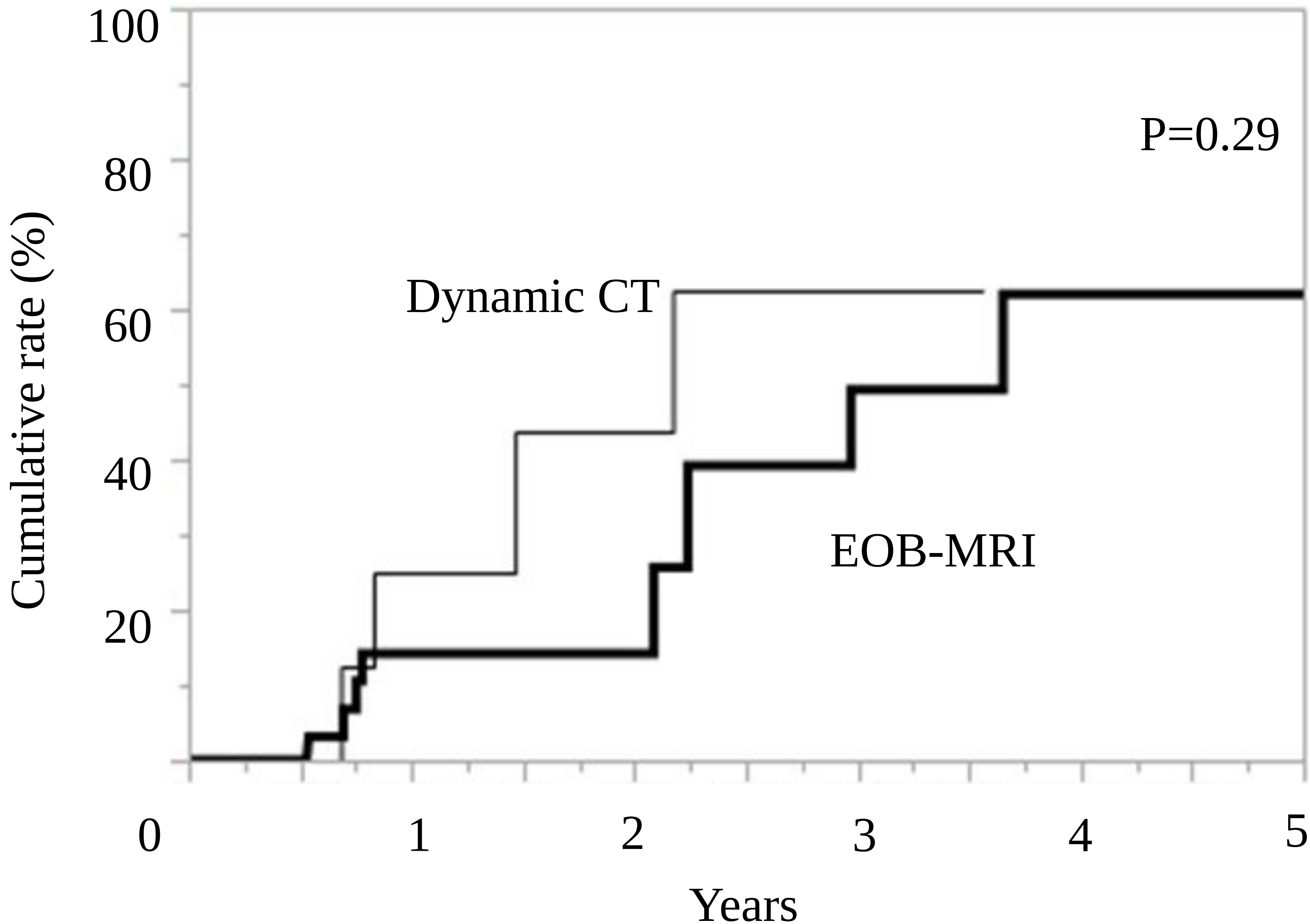


Fig. 3



100
80
60
40
20
0
Cumulative rate (%)
P=0.29
Dynamic CT
EOB-MRI
1
2
3
4
5
Years

Fig. 4

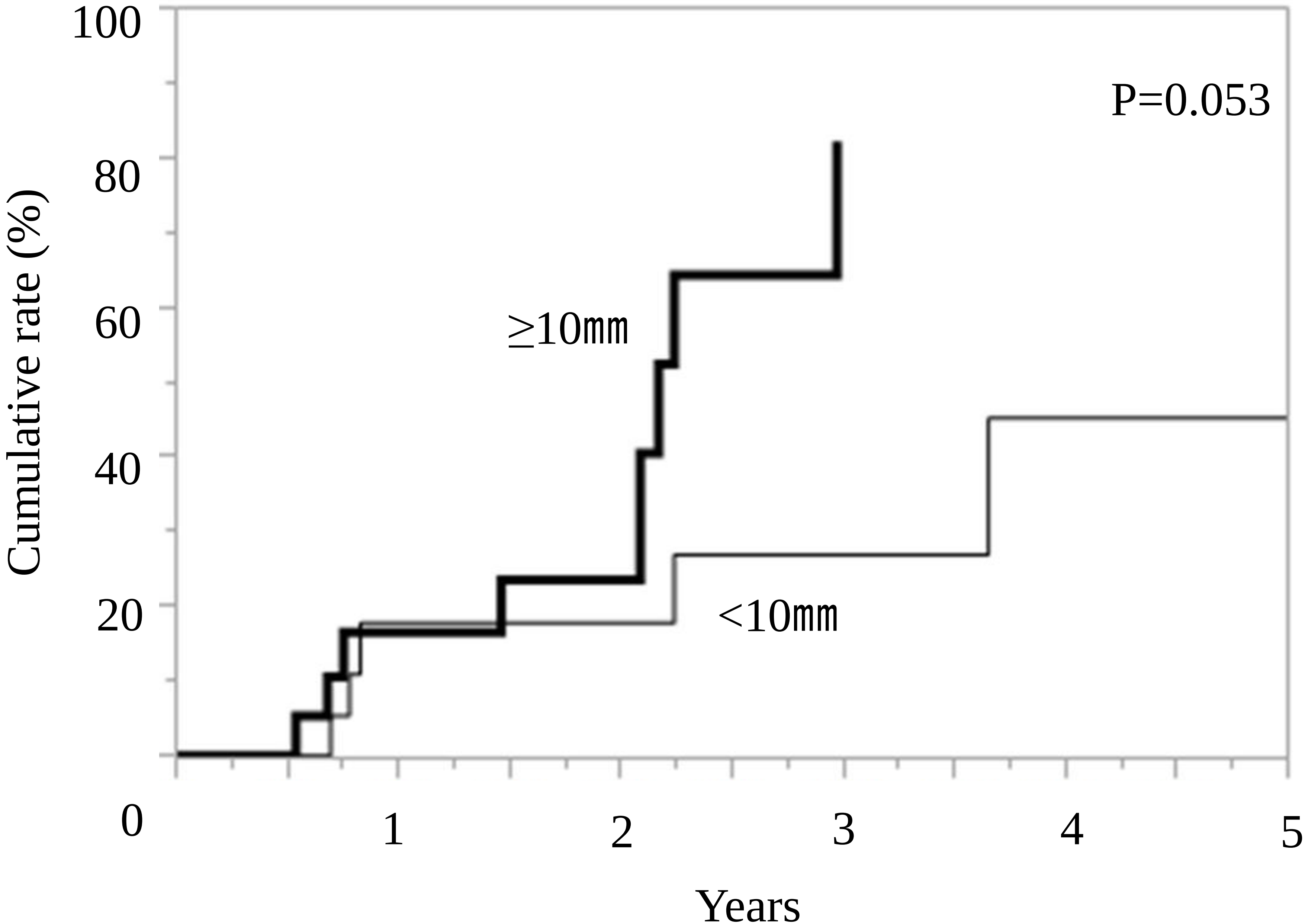
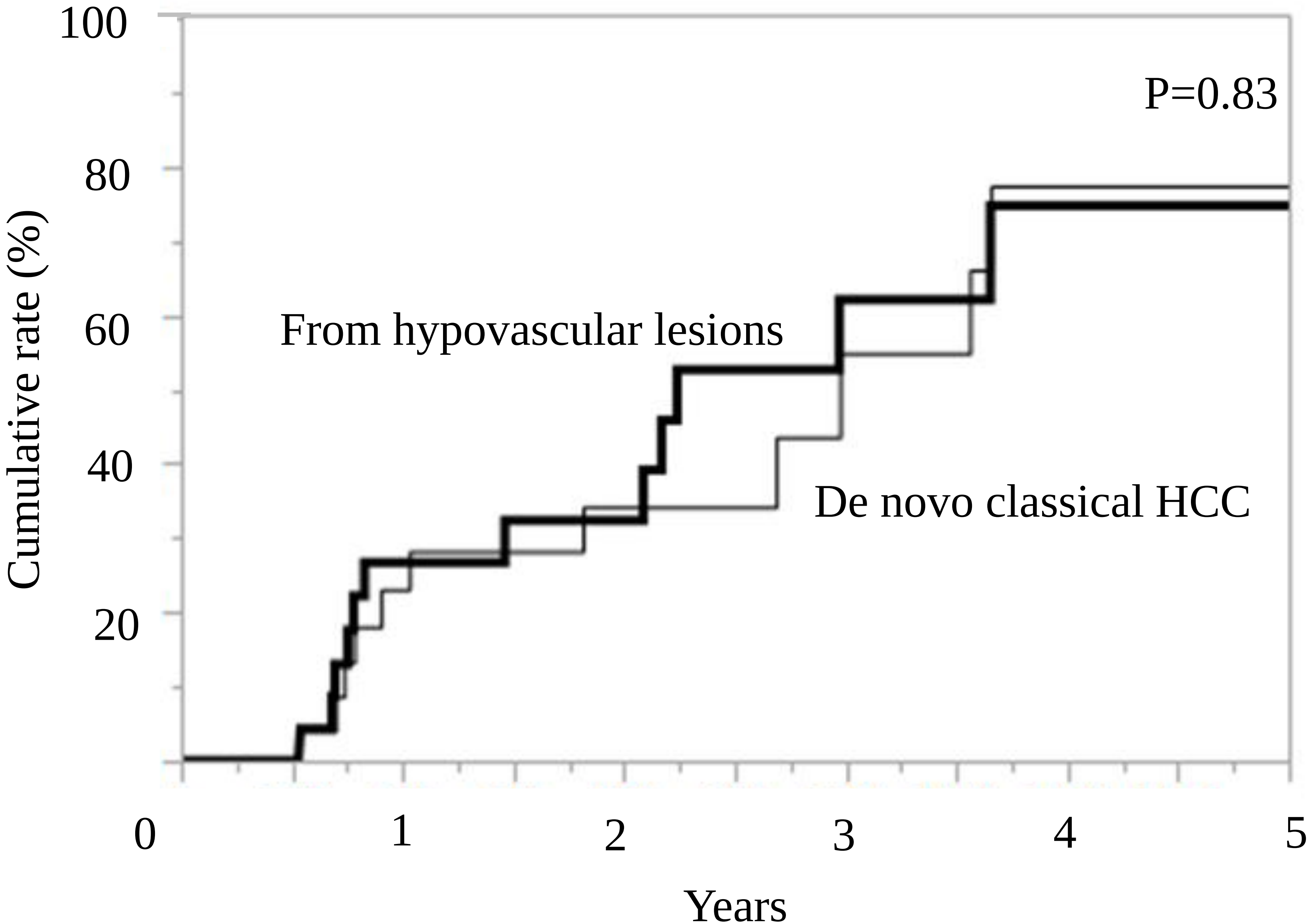


Fig. 5



100
80
60
40
20
Cumulative rate (%)
P=0.83
From hypovascular lesions
De novo classical HCC
0
1
2
3
4
5
Years

Fig. 6

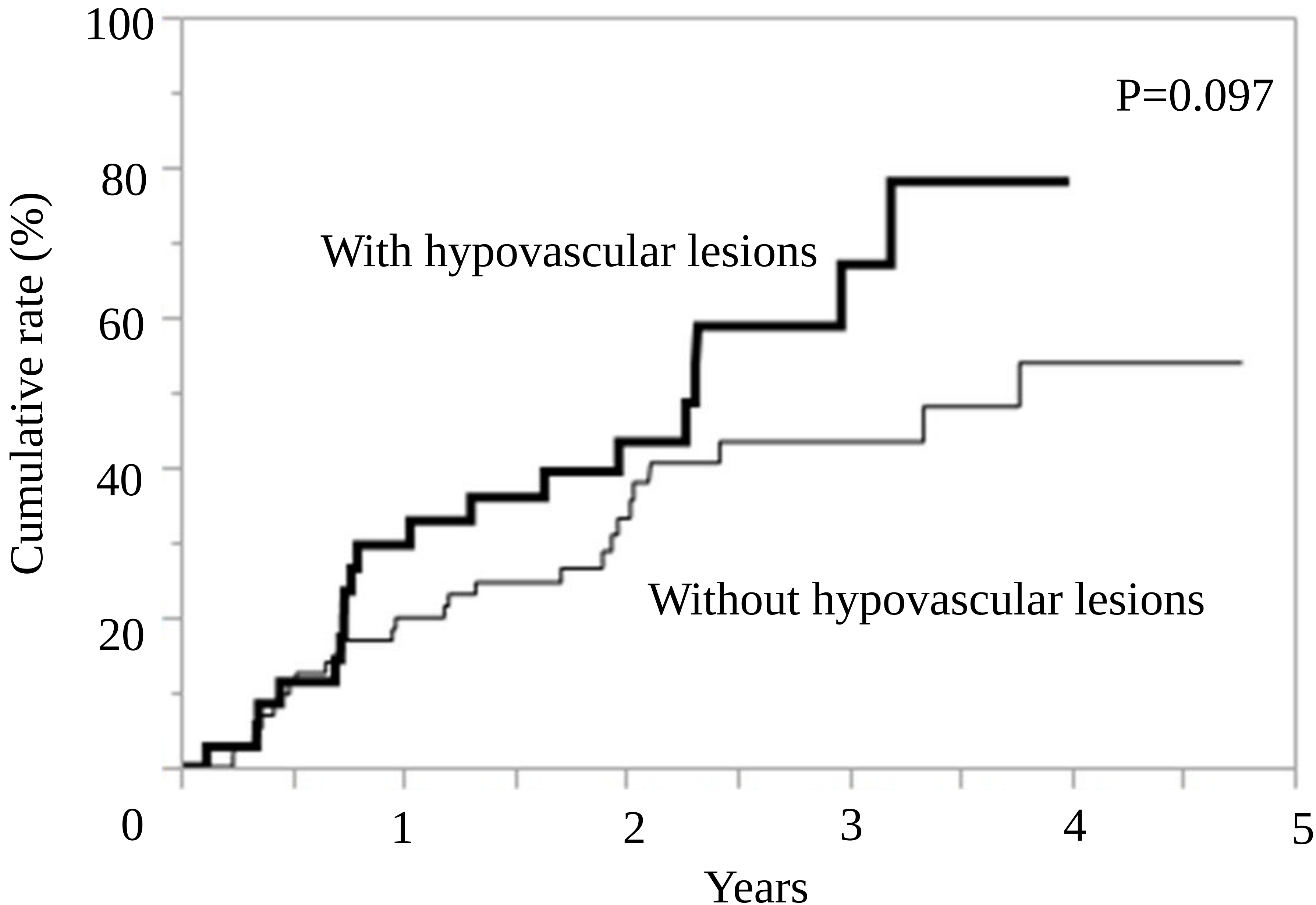
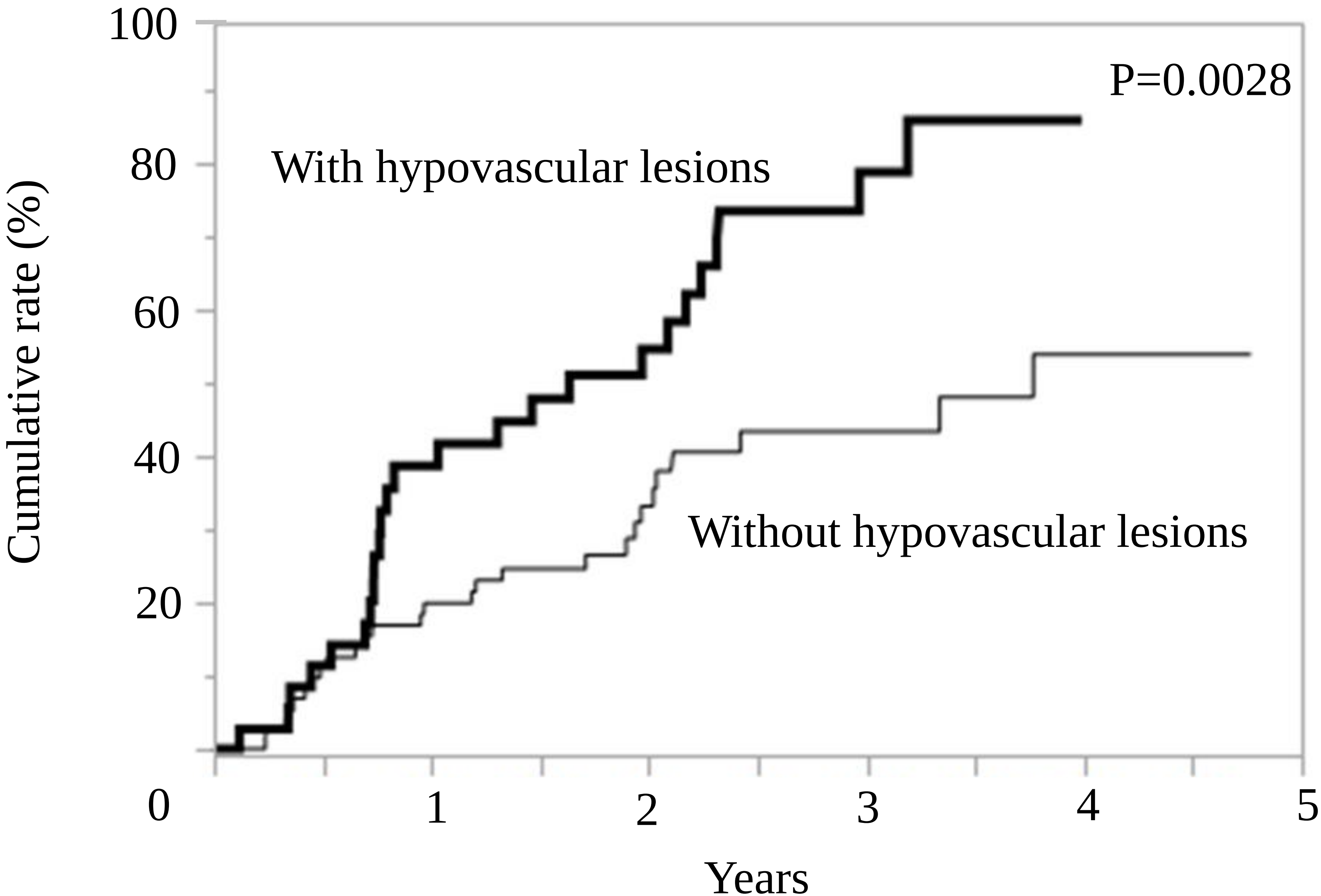
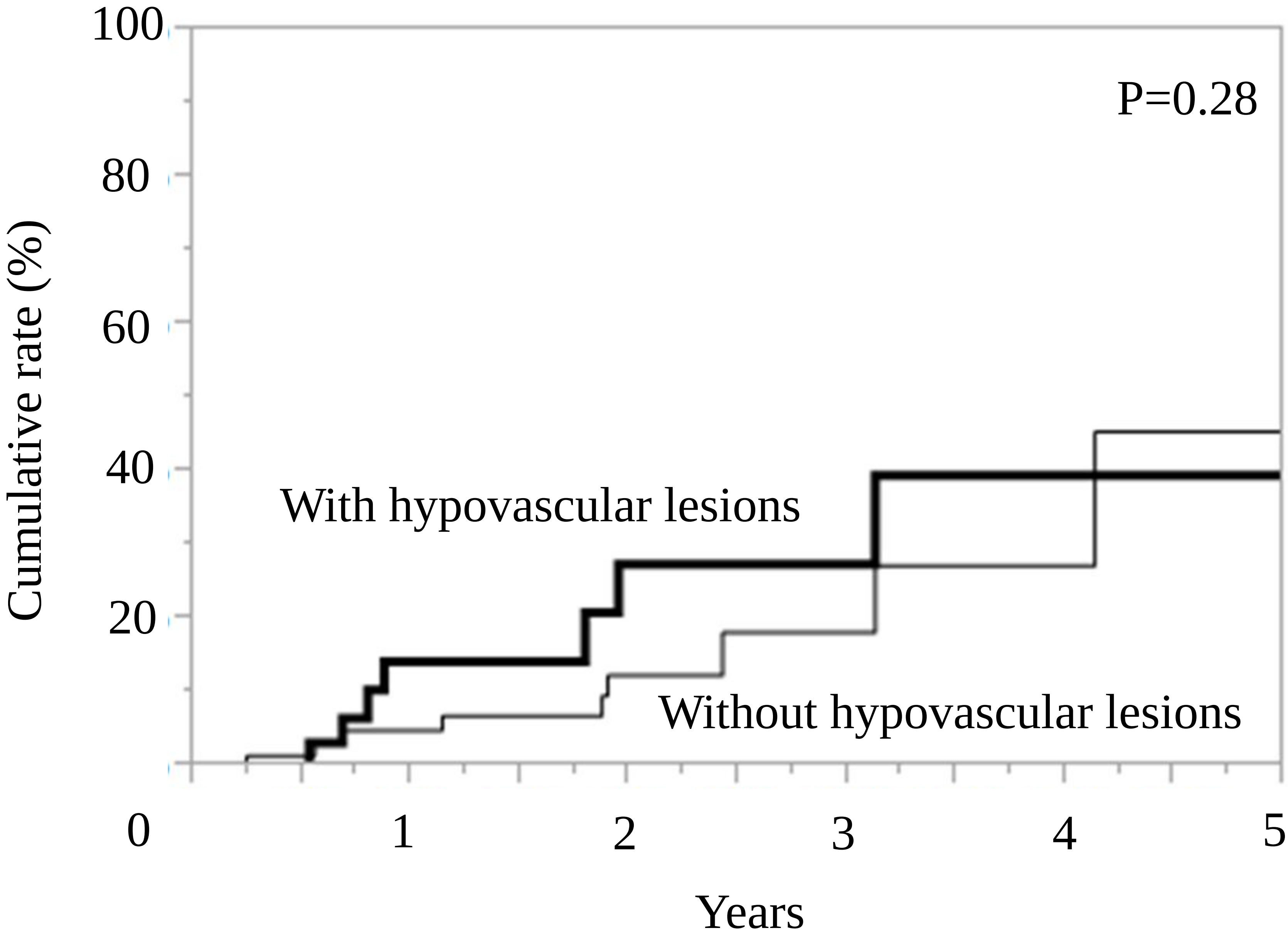

100
80
60
40
20
0
Cumulative rate (%)
P=0.097
With hypovascular lesions
Without hypovascular lesions
1
2
3
4
5
Years

Fig. 7



100
80
60
40
20
0
Cumulative rate (%)
P=0.0028
With hypovascular lesions
Without hypovascular lesions
1
2
3
4
5
Years

Fig. 8


P=0.28
With hypovascular lesions
Without hypovascular lesions
Cumulative rate (%)
100
80
60
40
20
0
1
2
3
4
5
Years