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► **To cite this version:**

Frédéric Marques, Mohammed Ghallab, Eric Vibert, Emmanuel Boleslawski, Olivier Soubrane, et al.. Prognostic Impact of Surgical Margins for Hepatocellular Carcinoma According to Preoperative Alpha-Fetoprotein Level.. HPB, 2022, 24 (6), pp.848–856. 10.1016/j.hpb.2021.10.012 . hal-03692960

**HAL Id: hal-03692960**

**<https://u-picardie.hal.science/hal-03692960v1>**

Submitted on 22 Jul 2024

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# **Prognostic impact of surgical margins for hepatocellular carcinoma according to preoperative alpha-fetoprotein level**

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Category: Original article, retrospective analysis of a prospective database

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#### FINANCIAL SUPPORT

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

#### DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose.

Running head : Impact of surgical margins and AFP in HCC

## INTRODUCTION

Surgical resection is a recommended curative treatment in patients with hepatocellular carcinoma (HCC) and well-preserved liver function (1-3). Curative resection for HCC implies surgical margins, and it should theoretically be as wide as 2 cm (4, 5). This width margin removes potential satellite nodules and/or peritumoral liver parenchyma that may contain microvascular invasion. In practice, large resection margins, particularly those more than 1 cm in width, are infrequently achieved in the surgical specimens. In such situations, it would be useful to identify preoperatively which patients require larger margins ( $> 1$  cm) and those patients who could be treated 'curatively' with a narrower margin ( $<1$ cm). These narrower margins could be justified by the tumour anatomical position or proximity to major vascular structures. They can also be considered to achieve parenchymal sparing in cirrhotic patients with decreased liver function. In such cases it would be important to identify preoperative characteristics that will allow for a smaller margin whilst still maintaining the aim to achieve a curative resection.

Alpha-fetoprotein (AFP) is a widespread, easy-to-use and reliable marker for HCC tumours. A high level of AFP ( $>100$  ng/ml) has been shown to predict pathological features associated with a poorer prognosis, such as satellite nodules and microvascular invasion (6-8). This variable has not been integrated in a more global algorithm to determine surgical management, particularly to enable achievement of narrow margins ( $<1$ cm) for HCC.

This study aims to evaluate whether a preoperative AFP level  $>100$  ng/ml impacts the prognostic role of surgical margin width in patients operated upon for HCC.

In this recent multicentric French surgical cohort, we first investigated whether  $>100$  ng/ml AFP was indeed correlating with negative pathological features as well as higher recurrence

rate. We then analysed the impact of resection margin in low- and high-AFP rate tumours—  
on time to recurrence and overall survival.

## MATERIAL AND METHODS

### *Study Design and Participants*

The present study derives from a larger prospectively designed, registered (clinicaltrials.gov NCT01715402) multicentre observational study investigating the objective and subjective determinants of the postoperative course after hepatectomy. It was deemed non-interventional by the ethical committees of participating institutions, approved by the French Advisory Committee on Information Processing in Material Research in the Field of Health (CCTIRS) and the agency for data protection and funded by the French Ministry of Health. Informed consent was obtained from participating patients. The present study specifically included all patients from April 2012 to January 2016 who underwent a first elective hepatectomy for HCC with curative intent in 5 tertiary hepatobiliary centres (Paul Brousse Hospital, Villejuif; Beaujon Hospital, Clichy; Claude Huriez Hospital, Lille; Edouard Herriot Hospital, Lyon and North Hospital, Amiens).

### *Data collection*

Values for preoperative AFP were available for 397 of 480 consecutive curative hepatectomies for HCC performed in these 5 centres within 30 days prior to surgery. The preoperative evaluation consisted of laboratory tests including liver function tests, imaging studies including ultrasonography, contrast-enhanced abdominal computer tomography  $\pm$  volumetry and magnetic resonance imaging. Liver resections were performed by laparoscopy or laparotomy when the MELD score was  $\leq 12$  and/or platelet counts were  $\geq 80 \times 10^9/L$ . Routine intraoperative ultrasonography was performed to guide liver resections. When feasible, anatomic resection was performed. Transarterial selective chemoembolization (TACE) followed by portal vein embolization (PVE) was the treatment strategy when planning major hepatectomies in patients with a pathological liver (9, 10). Postoperative

mortality was defined at 90 days. Unless postoperative death occurred, the minimal follow-up required was 1 month, and all patients were monitored every 4 months with CT and/or MRI along with biological tests including serum AFP and liver function. Liver decompensation and/or recurrences were treated by liver transplantation (LT) according to French AFP score (11, 12) in patients aged less than 70 years. In the absence of LT, recurrences were treated by redo hepatectomy, local destruction, TACE or systemic therapy.

Histopathological feature analyses included the number of tumours, their sizes, tumour differentiation grade, microvascular invasion and satellite nodules. These analyses also included investigations of non-tumoral parenchyma and resection margin measurement. In patients with more than one tumour, the minimal distance between any tumour and the surgical transection plane was considered. R1 resection was defined as margins <1mm. In tumours with more than one differentiation grade, the poorest grade was selected. Hepatocholangiocarcinoma type tumours were excluded from the analysis.

### *Study Endpoint*

The first part of this study involved determining whether a preoperative AFP level > 100 ng/mL (7, 11) impacted the recurrence for resectable HCC. Thereafter, we divided our study population into two groups: low ( $\leq 100$  ng/mL) and high (>100 ng/mL) AFP levels. Then, we assessed the impact of resection margins according to preoperative AFP level on survival. A resection margin <1 cm was defined as a narrow margin.

The primary endpoint of this study was the time to recurrence according to preoperative AFP level (low or high) and surgical margins (narrow or large). The secondary endpoint was overall survival according to preoperative AFP level and surgical margins.

Explanatory variables tested for time to recurrence and overall survival were demographic characteristics, platelet count, causes and severity of liver disease assessed by the MELD

score (13, 14), tumour size and number of tumours. The association of AFP > 100 ng/ml and resection margins was also tested.

### *Statistical analysis*

Data are shown as prevalence and means (standard deviation). Categorical variables were compared by the chi-squared test, and continuous variables were compared by the student's t-test. Survival curves were compared by the log-rank test. Prognostic factors were analysed by Cox proportional hazard regression analysis, using a stepwise procedure. The hazard ratio (HR) and 95% confidence interval (CI) are given. The factors with a  $p$ -value under 0.10 in univariate analysis were included in multivariate analysis. For all tests, statistical significance was defined as  $p < 0.05$ . Data were analysed using IBM SPSS 20.0 software (IBM, Armonk, NY).



## RESULTS

### *Patients Characteristics and outcomes*

397 patients did meet our selection criteria. These were operated on between April 2012 and January 2016, 397 in 5 university. The patients' demographic characteristics and histopathological features are summarized in Table 1. Underlying liver parenchyma was F3 in 73/397 (18.4%) and F4 in 183/397 (46.1%). The aetiology of the underlying liver disease was alcohol-related, hepatitis B virus (HBV) and hepatitis C virus (HCV) at a percentage of 32%, 15% and 23% respectively. An AFP level > 100 ng/mL was found in 98 patients (25%). The 90-day mortality rate was 3.8%. This was not statistically different between minor and major hepatectomy groups. The overall survival at 36 months was 80%, and the recurrence rate was 54% with a median follow-up of 25 months [1-59]. Liver transplantation was performed in 13 patients (3.3%) for HCC recurrence.

### *Demographic comparison and prognostic impact of resection margins*

Wide resection margin was defined at >1cm. This is the planned macroscopic surgical margin prior to histopathological analysis. In our study population, 150 patients (38%) had a wide resection margin (> 1 cm). No statistically significant difference was found in the demographic and clinical characteristics between patients with wide (>1cm) and narrow (<1cm) macroscopic margins. Similarly, there was no statistically significant difference in the aetiology and severity of liver disease between the two groups (Table 2). There was an observed increase in the mean size of the lesion in patients with narrow margins (6.6 vs 5.4 cm; p=0.017). More microvascular invasion was observed in the group with narrow margins (37 vs 26%; p=0.022). In our study population, sixty-seven patients (17%) had R1 resection margins (< 1 mm). Other histopathological features were not statistically different.

There was no observed impact of the macroscopic surgical resection margins on time to recurrence (Figure 1). Equally there was no observed statistically significant difference in the 90-day postoperative mortality between the narrow and wide-margin groups (4.5% vs 2.7%,  $p=0.365$ , respectively).

#### *Prognostic impact of AFP > 100 ng/mL*

A high preoperative AFP level (> 100 ng/mL) was recorded in 98 patients (25%). Table 3 summarizes the demographics, clinical and histopathological characteristics in the high AFP- and low-AFP groups. There were numerous clinical features such as age, gender, aetiology of liver disease, diabetes mellitus and presence of metabolic syndrome that had statistically significant difference between the high- and low-AFP groups. The severity of underlying liver disease evaluated by MELD score was not significantly different between the two groups (7.8 vs 8.0;  $p=0.461$ ). Macroscopic surgical resection margins, defined at 1cm, were not significantly different between the two groups (0.78 vs 0.88 cm;  $p=0.419$ ). Major hepatectomies were more frequently performed in patients with high-AFP patients than low-AFP ones (44% vs 30%;  $p=0.014$ ). No statistically significant postoperative mortality was observed between low- and high-AFP groups, 3.3% and 5.1% respectively ( $p=0.540$ ).

The high AFP level group was associated with worse histopathological features. Patients with high AFP had significantly larger tumours than low-AFP patients (7.7 vs 5.6 cm;  $p<0.001$ ). The high-AFP group also had more frequent microvascular invasions (43% vs 29%;  $p=0.01$ ), satellite nodules (35% vs 22%;  $p=0.013$ ) and poorly differentiated tumours (18% vs 9%;  $p=0.014$ ).

Patients with a high AFP level had a shorter time to recurrence than low-AFP patients ( $p<0.001$ ). In the high-AFP group, 1- and 3-year recurrence rates were respectively 52% and 61%. In the low-AFP group, these rates were 21% and 52%, respectively (Figure 2).

Patients with high levels of AFP had a significantly worse overall survival than those with low AFP ( $p=0.015$ ).

*Impact of surgical resection margins according to preoperative AFP level on recurrence and survival*

In the low-AFP group, patients with narrow resection margins ( $< 1$  cm) had an estimated median time to recurrence of 36 months, and patients with wide resection margins ( $\geq 1$  cm) had an estimated median time to recurrence of 34 months ( $p=0.756$ ). Time-to-recurrence curves for the low-AFP group are shown in Figure 3a.

In the high-AFP group, patients with narrow margins had a significantly higher recurrence rate than those with wide margins ( $p=0.016$ ). The estimated median time to recurrence for patients with narrow margins was 8 months, whereas this point was not reached for patients with wide margins. Time-to-recurrence curves are shown in Figure 3b.

We analysed preoperative factors associated with a shorter time to recurrence (Table 4). A preoperative AFP level  $> 100$  ng/mL with margins  $<1$  cm was an independent factor found in multivariate analysis (HR=2.243, CI95% [1.581-3.181],  $p<0.001$ ), along with tumour size and number.

In the low-AFP group, no statistically significant difference was observed in overall survivals between patients with narrow vs wide resection margins ( $p=0.079$ ; Figure 4a). Moreover, 42% of deaths occurred without HCC recurrence in the low AFP group.

In the high-AFP group, worse overall survival was observed in patients with narrow margins ( $p=0.043$ ; Figure 4b). In addition, only 13% of deaths occurred without HCC recurrence in the high AFP group.

Preoperative factors associated with overall mortality were analysed. (Table 5). A preoperative AFP level  $> 100$  ng/mL with margins  $<1$  cm was an independent factor found in

multivariate analysis (HR=2.076, CI95% [1.198-3.598],  $p<0.009$ ), along with the number of tumours.

#### *Patterns and treatments of recurrence*

With a median follow-up of 25 [1–59] months, tumour recurrence was observed in 183 patients (46%). 120 patients had liver-only recurrence during follow-up, accounting for 66% of recurrences. Data on exact site of recurrence within the liver was not available. Tumour recurrence at metastatic sites occurred in the lungs (10%), lymph nodes (6%), in bones (5%) and in adrenal glands (4%). Treatment with a curative intent was administered in 36% of patients with recurrence. Patients with high AFP and margins <1 cm had less frequent liver-only recurrence than other patients (52% vs 70%;  $p=0.033$ ). They also underwent less frequent curative treatment for the recurrence than other patients (21% vs 41%;  $p=0.022$ ).

## DISCUSSION

### *Statement of Principal Findings*

Data from our study showed that AFP > 100 ng/mL combined with narrow surgical margins <1 cm was an independent risk factor of HCC recurrence. This combined factor impacted time to recurrence as well as overall survival. In these patients with aggressive HCC and a high rate of early recurrences, the presence of wide resection margins did impact long-term survival.

On Kaplan-Meier analysis for time to recurrence in the high-AFP group with wide margins, tumour recurrence was only observed till 17 months. No recurrence occurred after 17 months. This was an interesting observation, where we think the implied disease aggressiveness dictates that in our small patient group, all events of tumour recurrence did occur in the first 17 months. This is consistent with known fact that generally speaking, HCC patients tend to recur early(15). In the high AFP group, the larger (>1cm) macroscopic surgical resection margin mainly positively impacted long-term survival despite not always preventing early recurrences.

### *Strength and weakness of the study*

This study benefited from a large multicentric design, using a prospective cohort of patients from 5 HPB tertiary centres in France. The cohort of patients studied who were included in a short and recent period of time. Preoperative and intraoperative management were similar in all centres following national and European guidelines. Postoperative data were also collected homogeneously among the 5 centres. Recurrence treatments and indications for liver transplantation were the same in all study centres.

Using a prospective database can cause limitations in some findings. In our database liver function was assessed with MELD and Child-Pugh scores. Other means of liver assessment,

such as transient ultrasonography (16) or portal gradient, were unavailable. As with any multicentric studies, some heterogeneity in applied technology and HCC treatment strategies were observed. Some centres performed transient elastography and indocyanine green tests preoperatively to select patients. Hence, this could have caused a selection bias between the study centres.

Intraoperative surgical techniques for liver resection were performed at the discretion of operating surgeons. The use of ultrasonic devices or argon beam coagulation was not documented and could have impacted the quality of resection margins (17). Macroscopic resection margin assessment was performed in each centre according to local practices, and the extent of tumoral necrosis was unknown.

We included all consecutive patients who underwent a first resection for HCC, regardless of other previous treatments because we know, for instance, that neoadjuvant sequential trans-arterial chemoembolization and portal vein embolization before major hepatectomies improve outcomes after liver resection (10, 18). Non-surgical preoperative treatment was not an exclusion criterion and could have influenced outcomes for some patients of our study, even if all study centres had the same standards of treatment during this short and recent period of inclusion. We also did not consider histopathological response to preoperative treatments such as tumour necrosis.

In other studies, anatomical resections improved outcomes after hepatectomy for HCC (19, 20). In all study centres, anatomical resection was performed when feasible, but our database did not consider whether liver resections were anatomical. Therefore, we could not analyse which one of anatomical resection or wide resection margins influenced survival outcomes the most. This would be an interesting question to answer in future prospective studies.

The possibility for wide resection margins depends sometimes on HCC location, and it must be taken into account before deciding on treatment allocation (3). In our database, we did not

have information on exact tumour location. Furthermore, in patients whose histology analysis reported R1 resections, we could not differentiate between they were standard parenchymal R1 margins and those with proximity to vascular structures. This being a known prognostic factor in colorectal liver metastases (21).

One important limitation is the absolute number of the patients in the high AFP group. This was only 25% of the cohort. This is consistent with recently published data, that patients with normal or low AFP represent the majority of resected patients with HCC(22). However, it is still an important limitation to consider.

#### *Interpretation with reference to other studies*

Hepatic resection with appropriate surgical margins is a first-line curative treatment in patients with a single HCC and good liver function (1-3). The most recent European recommendations (3) for the management of HCC consider performance status and liver function and these factors determine whether patients can have surgery or not and also influence long-term survival. The current recommendations do not consider tumour aggressiveness or location, which are prevailing factors for early intra- or extra-hepatic recurrence. Wide surgical margins, which highly impact oncological and survival outcomes (5), are not always achievable because of altered liver function or due to spare hepatic parenchyma (23). Our aim in this study was to bridge these two gaps, the tumour aggressiveness, and surgical margins. The data observed in this study showed that tumours associated with a high preoperative AFP level (> 100 ng/mL) resected with a wide margin have less recurrence. The resection margin did not impact survival or recurrence in patients with low preoperative AFP. Other studies (7, 24) demonstrated a benefit in anatomic resection in tumours with high levels of biological markers such as AFP. But to our

knowledge, no other study assessed the impact of surgical margins according to preoperative AFP level.

This result is sustained by the fact that in our study, a preoperative AFP level > 100 ng/mL was associated with invasive pathological features such as microvascular invasion, satellite nodules and poorer tumour differentiation. Other authors found a similar association between a high AFP level and poor pathological features (6, 7). These features of tumour aggressiveness and invasive pathological features were associated with poorer oncological and survival outcomes.

Preoperative assessment of tumour aggressiveness is a matter of interest to guide the extension of surgical resection. Other authors focused on different assessment methods, such as <sup>18</sup>F fluorodeoxyglucose positron emission tomography and computed tomography (<sup>18</sup>F-FDG PET-CT). Studies showed that this method had low sensitivity for HCC but, when positive, it is highly associated with tumour aggressiveness (25) and can accurately predict outcomes after HCC treatment. More specifically, some authors studied the impact of surgical margins according to <sup>18</sup>F-FDG PET-CT, and when this method led to a positive result, patients with wide surgical margins (>1cm) had a better outcome than those with narrow margins. Margins did not impact disease-free or overall survival in patients who were negative upon <sup>18</sup>F-FDG PET CT(26).

Based on the number of patients in our study and the study design it is difficult to confirm that the observations made in patients with high AFP is not confounded by other factors.

All these criteria should aim at recognizing highly aggressive tumours that could benefit from surgical resection with wide margins rather than local ablative treatments. As shown in other studies, radiofrequency ablation is a curative treatment only for small HCC because of local tumour progression due to untreated satellite nodules (27). A high AFP level has also



consistently been a negative prognostic factor in several studies evaluating the effectiveness of radiofrequency ablation on long-term outcomes (28-31). An explanation was brought by some authors who have shown that high a AFP level was correlated to microvascular invasion and accurately predicted local recurrence after RFA (8).

## CONCLUSIONS

Preoperative AFP level with a cut off value of 100ng/mL is an important factor to be considered in the planning of HCC management and determining of operative surgical margins. It does offer a simple and non-invasive measure to risk stratify the patients and predict outcome based on the data observed in this study. Even considering that the preoperative high AFP value is a surrogate to other histological and tumour biology features, these are only available to the surgeons after the die is cast. A simple adjustment to current practice would be offering these high-risk patients and macroscopic resection margin >1cm and perhaps adjust the postoperative surveillance program they are offered. We have observed that in low-AFP tumours, the larger surgical margins did not impact recurrence-free or overall survival. The data numbers and study design does not mean that we can recommend offering these patients a smaller resection margin. However, this should be carefully assessed, and other poor prognostic factors should be considered. It is noted however this is a lesser risk group and outcomes can be similar with high or low margins. A useful information that can help dictate treatment choice such as offering limited resections or radiofrequency ablations for small tumours if liver function or tumour locations do not allow wider margins.

The first hepatectomy for HCC is important because recurrence is often more difficult to treat (32, 33), and salvage transplantation is less efficient than primary liver transplantation (34, 35). Equally the treatment strategy is different than that of colorectal liver metastases that favours more parenchymal preservation based on current knowledge of tumour biology and

available chemotherapy agents. For high-AFP tumours, if margins are not achievable because of an important parenchyma sacrifice or anatomical reasons, other treatments such as liver transplantation in successfully down-staged or oncologically controlled patients should be considered (36). A particular caution should be taken in elderly patients because salvage liver transplantation might not be feasible.

## REFERENCES

1. Verslype C, Rosmorduc O, Rougier P, Group EGW. Hepatocellular carcinoma: ESMO-ESDO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of oncology : official journal of the European Society for Medical Oncology*. 2012;23 Suppl 7:vii41-8.
2. Manzini G, Henne-Bruns D, Porzsolt F, Kremer M. Is there a standard for surgical therapy of hepatocellular carcinoma in healthy and cirrhotic liver? A comparison of eight guidelines. *BMJ open gastroenterology*. 2017;4(1):e000129.
3. European Association for the Study of the Liver. Electronic address eee, European Association for the Study of the L. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. *Journal of hepatology*. 2018;69(1):182-236.
4. Nakashima T, Kojiro M. Pathologic characteristics of hepatocellular carcinoma. *Seminars in liver disease*. 1986;6(3):259-66.
5. Shi M, Guo RP, Lin XJ, Zhang YQ, Chen MS, Zhang CQ, et al. Partial hepatectomy with wide versus narrow resection margin for solitary hepatocellular carcinoma: a prospective randomized trial. *Annals of surgery*. 2007;245(1):36-43.
6. Chan SL, Chan AT, Yeo W. Role of alpha-fetoprotein in hepatocellular carcinoma: prognostication, treatment monitoring or both? *Future oncology*. 2009;5(6):889-99.
7. Fan LF, Zhao WC, Yang N, Yang GS. Alpha-fetoprotein: the predictor of microvascular invasion in solitary small hepatocellular carcinoma and criterion for anatomic or non-anatomic hepatic resection. *Hepato-gastroenterology*. 2013;60(124):825-36.

8. Imai K, Yamashita YI, Yusa T, Nakao Y, Itoyama R, Nakagawa S, et al. Microvascular Invasion in Small-sized Hepatocellular Carcinoma: Significance for Outcomes Following Hepatectomy and Radiofrequency Ablation. *Anticancer research*. 2018;38(2):1053-60.
9. Yoo H, Kim JH, Ko GY, Kim KW, Gwon DI, Lee SG, et al. Sequential transcatheter arterial chemoembolization and portal vein embolization versus portal vein embolization only before major hepatectomy for patients with hepatocellular carcinoma. *Annals of surgical oncology*. 2011;18(5):1251-7.
10. Ronot M, Cauchy F, Gregoli B, Breguet R, Allaham W, Paradis V, et al. Sequential transarterial chemoembolization and portal vein embolization before resection is a valid oncological strategy for unilobar hepatocellular carcinoma regardless of the tumor burden. *HPB : the official journal of the International Hepato Pancreato Biliary Association*. 2016;18(8):684-90.
11. Duvoux C, Roudot-Thoraval F, Decaens T, Pessione F, Badran H, Piardi T, et al. Liver transplantation for hepatocellular carcinoma: a model including alpha-fetoprotein improves the performance of Milan criteria. *Gastroenterology*. 2012;143(4):986-94 e3; quiz e14-5.
12. Notarpaolo A, Layese R, Magistri P, Gambato M, Colledan M, Magini G, et al. Validation of the AFP model as a predictor of HCC recurrence in patients with viral hepatitis-related cirrhosis who had received a liver transplant for HCC. *Journal of hepatology*. 2017;66(3):552-9.
13. Malinchoc M, Kamath PS, Gordon FD, Peine CJ, Rank J, ter Borg PC. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. *Hepatology*. 2000;31(4):864-71.
14. Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, et al. A model to predict survival in patients with end-stage liver disease. *Hepatology*. 2001;33(2):464-70.
15. Gelli M, Sebah M, Porcher R, Romanelli E, Vibert E, Sa Cunha A, et al. Liver Resection for Early Hepatocellular Carcinoma: Preoperative Predictors of Non Transplantable Recurrence and Implications for Treatment Allocation. *Ann Surg*. 2020;272(5):820-6.

16. Rajakannu M, Coilly A, Adam R, Samuel D, Vibert E. Prospective validation of transient elastography for staging liver fibrosis in patients undergoing hepatectomy and liver transplantation. *Journal of hepatology*. 2017.
17. Katkhouda N Fau - Friedlander M, Friedlander M Fau - Darehzereshki A, Darehzereshki A Fau - Mason RJ, Mason Rj Fau - Zehetner J, Zehetner J Fau - Moazzez A, Moazzez A Fau - Chan LS, et al. Argon beam coagulation versus fibrin sealant for hemostasis following liver resection: a randomized study in a porcine model. (0172-6390 (Print)).
18. Aoki T, Imamura H, Hasegawa K, Matsukura A, Sano K, Sugawara Y, et al. Sequential preoperative arterial and portal venous embolizations in patients with hepatocellular carcinoma. *Archives of surgery*. 2004;139(7):766-74.
19. Zhou Y, Xu D, Wu L, Li B. Meta-analysis of anatomic resection versus nonanatomic resection for hepatocellular carcinoma. *Langenbeck's archives of surgery*. 2011;396(7):1109-17.
20. Cucchetti A, Cescon M, Ercolani G, Bigonzi E, Torzilli G, Pinna AD. A comprehensive meta-regression analysis on outcome of anatomic resection versus nonanatomic resection for hepatocellular carcinoma. *Annals of surgical oncology*. 2012;19(12):3697-705.
21. Vigano L, Procopio F, Cimino MM, Donadon M, Gatti A, Costa G, et al. Is Tumor Detachment from Vascular Structures Equivalent to R0 Resection in Surgery for Colorectal Liver Metastases? An Observational Cohort. *Annals of surgical oncology*. 2016;23(4):1352-60.
22. Carr BI, Akkiz H, Üsküdar O, Yalçın K, Guerra V, Kuran S, et al. HCC with low- and normal-serum alpha-fetoprotein levels. *Clin Pract (Lond)*. 2018;15(1):453-64.
23. Kingham TP, Correa-Gallego C, D'Angelica MI, Gonen M, DeMatteo RP, Fong Y, et al. Hepatic parenchymal preservation surgery: decreasing morbidity and mortality rates in 4,152 resections for malignancy. *Journal of the American College of Surgeons*. 2015;220(4):471-9.
24. Jung DH, Hwang S, Lee YJ, Kim KH, Song GW, Ahn CS, et al. Small Hepatocellular Carcinoma With Low Tumor Marker Expression Benefits More From Anatomical Resection Than Tumors With Aggressive Biology. *Annals of surgery*. 2017.

25. Asman Y, Evenson AR, Even-Sapir E, Shibolet O. [18F]fludeoxyglucose positron emission tomography and computed tomography as a prognostic tool before liver transplantation, resection, and loco-ablative therapies for hepatocellular carcinoma. *Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society*. 2015;21(5):572-80.
26. Park JH, Kim DH, Kim SH, Kim MY, Baik SK, Hong IS. The Clinical Implications of Liver Resection Margin Size in Patients with Hepatocellular Carcinoma in Terms of Positron Emission Tomography Positivity. *World journal of surgery*. 2018;42(5):1514-22.
27. Hocquelet A, Aube C, Rode A, Cartier V, Sutter O, Manichon AF, et al. Comparison of no-touch multi-bipolar vs. monopolar radiofrequency ablation for small HCC. *Journal of hepatology*. 2017;66(1):67-74.
28. Dohi C, Nouse K, Miyahara K, Morimoto Y, Wada N, Kinugasa H, et al. Potential of alpha-fetoprotein as a prognostic marker after curative radiofrequency ablation of hepatocellular carcinoma. *Hepatology research : the official journal of the Japan Society of Hepatology*. 2016;46(9):916-23.
29. Seror O, N'Kontchou G, Nault JC, Rabahi Y, Nahon P, Ganne-Carrie N, et al. Hepatocellular Carcinoma within Milan Criteria: No-Touch Multibipolar Radiofrequency Ablation for Treatment-Long-term Results. *Radiology*. 2016;280:611-21.
30. Yu SJ, Kwon JH, Kim W, Yoon JH, Lee JM, Lee JY, et al. Initial Alpha-Fetoprotein Response Predicts Prognosis in Hepatitis B-related Solitary HCC Patients After Radiofrequency Ablation. *Journal of clinical gastroenterology*. 2018;52(3):e18-e26.
31. Allaire M, Rekik S, Layese R, Mumana A, Guyot E, Nkontchou G, et al. Virologic control and severity of liver disease determine survival after radiofrequency ablation of hepatocellular carcinoma on cirrhosis. *Digestive and liver disease : official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver*. 2019;51(1):86-94.
32. Poon RT, Fan ST, Lo CM, Liu CL, Wong J. Intrahepatic recurrence after curative resection of hepatocellular carcinoma: long-term results of treatment and prognostic factors. *Annals of surgery*. 1999;229(2):216-22.
33. Poon RT-P, Fan ST, Lo CM, Liu CL, Wong J. Long-Term Survival and Pattern of Recurrence After Resection of Small Hepatocellular Carcinoma in Patients With Preserved

Liver Function: Implications for a Strategy of Salvage Transplantation. *Annals of surgery*. 2002;235(3):373-82.

34. Hu Z, Wang W, Li Z, Ye S, Zheng SS. Recipient outcomes of salvage liver transplantation versus primary liver transplantation: a systematic review and meta-analysis. *Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society*. 2012;18(11):1316-23.

35. Bhangui P, Allard MA, Vibert E, Cherqui D, Pelletier G, Cunha AS, et al. Salvage Versus Primary Liver Transplantation for Early Hepatocellular Carcinoma: Do Both Strategies Yield Similar Outcomes? *Annals of surgery*. 2016;264(1):155-63.

36. Vibert E, Azoulay D, Hoti E, Iacopinelli S, Samuel D, Salloum C, et al. Progression of alpha-fetoprotein before liver transplantation for hepatocellular carcinoma in cirrhotic patients: a critical factor. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons*. 2010;10(1):129-37.

## Figure Legends

**Figure 1** : Impact of surgical margins on time-to-recurrence after hepatectomy for HCC

**Figure 2** : Impact of surgical margins on time-to-recurrence according to AFP rate

**Figures 3a and 3b** : Impact of resection margins on time-to-recurrence according to AFP rate  $\leq 100$ ng/mL and  $>100$  ng/mL

**Figures 4a and 4b** : Impact of resection margins on overall survival according to AFP rate  $\leq 100$ ng/mL and  $>100$  ng/mL

**Table 1.** Demographic, biological and histopathological characteristics

<b>N = 397</b>	
Gender M/F	317/80
Age, mean ( $\pm$ SD)	64 ( $\pm$ 11)
AFP > 100 ng/mL	25 %
MELD score	7.9 ( $\pm$ 2.5)
Major hepatectomies	34%
Unifocal tumor	80%
Tumor size (cm), mean ( $\pm$ SD)	6.1 $\pm$ 4.8
Surgical margins < 1 cm	62%
F4 fibrosis	46%

AFP indicates alpha-fetoprotein; MELD, Model for End-stage Liver Disease; SD, Standard Deviation



**Table 2.** Demographic, clinical and histopathological characteristics according to surgical resection margins

	<b>Margins &lt; 1cm</b>	<b>Margins ≥ 1cm</b>	<b>p</b>
	<b>N = 247</b>	<b>N = 150</b>	
Gender M/F	193/54	124/26	0.275
Age, mean ± SD	63 ± 11	63 ± 11	0.543
Cirrhosis	51%	45%	0.328
Diabetes mellitus	30%	37%	0.142
HCV	22%	24%	0.739
HBV	15%	15%	0.950
Alcohol	29%	37%	0.084
Metabolic syndrome	24%	30%	158
MELD score, mean ± SD	8.1 ± 2.6	7.6 ± 2.3	0.073
Major hepatectomies	37%	28%	0.093
Number of tumors, mean ± SD	1.3 ± 0.6	1.2 ± 0.6	0.351
Tumor size (cm), mean ± SD	6.6 ± 5.0	5.4 ± 4.2	<b>0.017</b>
Preoperative AFP > 100 ng/mL	27%	21%	0.148
Microvascular invasion	37%	26%	<b>0.022</b>
Satellite nodules	29%	20%	0.050
Poorly differentiated tumors	13%	8%	0.094

AFP indicates alpha-fetoprotein; SD, Standard Deviation; MELD, Model for End-stage Liver Disease

Variables in bold are statistically significant (p<0.05)

**Table 3.** Demographic, clinical and histopathological characteristics according to preoperative AFP rate

	<b>AFP ≤ 100</b>	<b>AFP &gt; 100</b>	<b>p</b>
	<b>N = 299</b>	<b>N = 98</b>	
Gender M/F	252/47	65/33	<b>&lt;0.001</b>
Age, mean (± SD)	65 (± 11)	60 (± 12)	<b>&lt;0.001</b>
Cirrhosis	54%	45%	0.139
Diabetes mellitus	37%	18%	<b>0.001</b>
HCV	23%	21%	0.593
HBV	10%	31%	<b>&lt;0.001</b>
Alcohol	35%	22%	<b>0.023</b>
Metabolic syndrome	29%	16%	<b>0.012</b>
MELD score, mean (±SD)	8.0 (± 2.5)	7.8 (± 2.3)	0.461
Major hepatectomies	30%	44%	<b>0.014</b>
Number of tumors, mean (± SD)	1.2 (± 0.6)	1.4(± 0.7)	0.115
Tumor size (cm), mean (± SD)	5.6 (± 4.4)	7.7 (± 5.5)	<b>0.001</b>
Surgical margins < 1 cm	60%	68%	0.148
Microvascular invasion	29%	43%	<b>0.010</b>
Satellite nodules	22%	35%	<b>0.013</b>
Poorly differentiated tumors	9%	18%	<b>0.014</b>
R1 resection	17%	16%	0.867

AFP indicates alpha-fetoprotein; SD, Standard Deviation; MELD, Model for End-stage Liver Disease

Variables in bold are statistically significant (p<0.05)

**Table 4.** Univariate and multivariate analysis of preoperative factors associated with a shorter time to recurrence

	Univariate			Multivariate		
	HR	95% CI	p	HR	95% CI	p
Diabetes mellitus			0.721			
HCV			0.057	1.227	0.828-1.819	0.308
HBV			0.353			
Metabolic syndrome			0.758			
Alcohol			0.697			
Cirrhosis			0.537			
Gender			0.576			
Age	1.010	0.997-1.024	0.118			
MELD score	1,034	0.978-1,092	0.236			
Platelets	1,001	1.000-1,003	0.115			
Tumor size	1.072	1.041-1.105	<b>&lt;0.001</b>	1.064	1.031-1.098	<b>&lt;0.001</b>
Number of tumors	1.457	1.179-1.800	<b>&lt;0.001</b>	1.483	1.197-1.839	<b>&lt;0.001</b>
AFP > 100 ng/mL and margins <1 cm			<b>&lt;0.001</b>	2.243	1.581-3.181	<b>&lt;0.001</b>

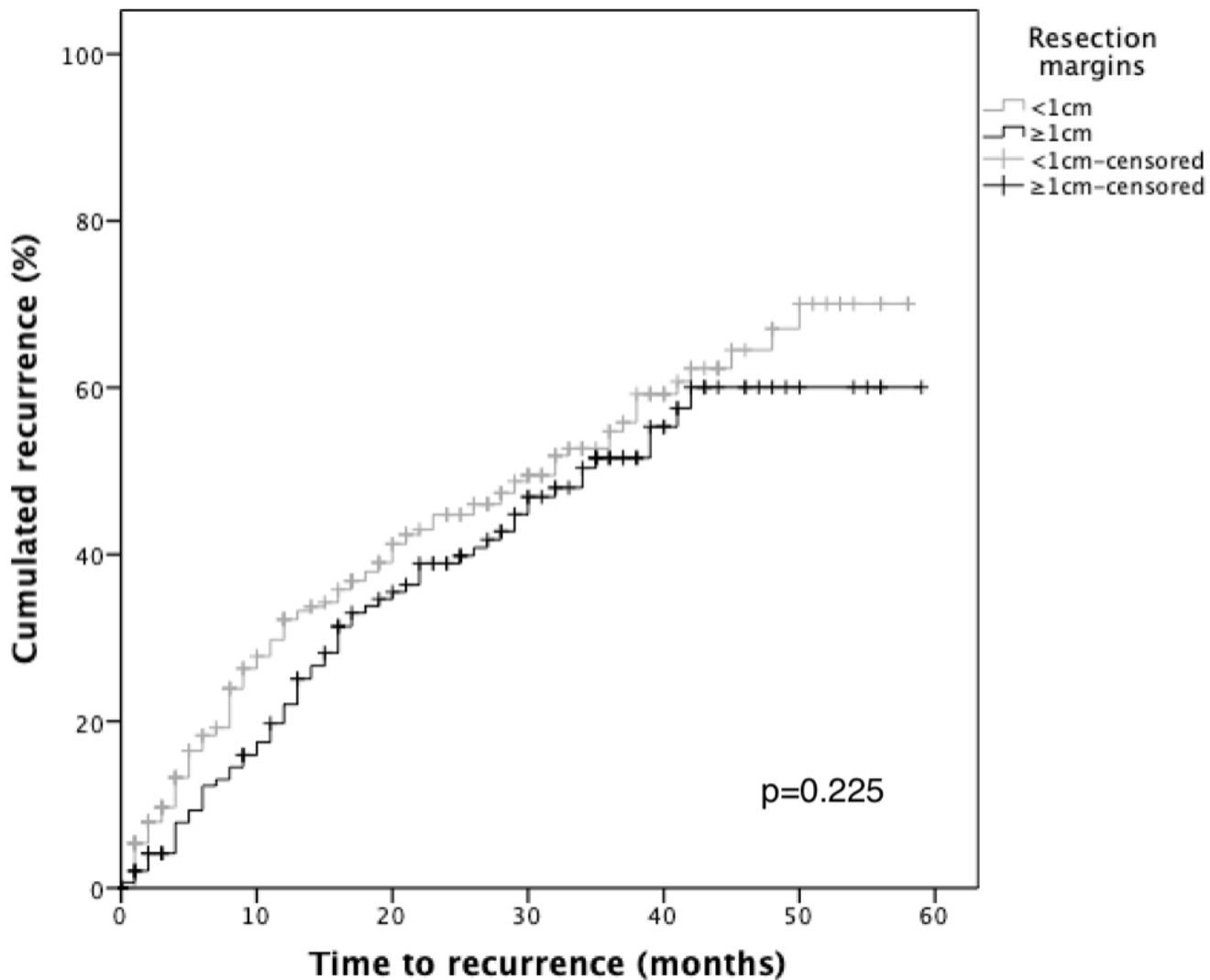
HR indicates Hazard ratio; CI, confidence interval; HCV, hepatitis C virus; HBV, hepatitis B virus; MELD, Model for End-stage Liver Disease(9, 10); AFP , alpha-fetoprotein

**Table 5.** Univariate and multivariate analysis of preoperative factors associated with overall mortality

	Univariate			Multivariate		
	HR	95% CI	p	HR	95% CI	p
Diabetes mellitus			<b>0.041</b>	1.568	0.856-2.872	0.146
HCV			0.651			
HBV			0.552			
Metabolic syndrome			0.283			
Alcohol			0.235			
Cirrhosis			0.534			
Gender F			<b>0.033</b>	1.604	0.929-2.770	0.09
Age	1.008	0.986-1.030	0.479			
MELD score	1,045	0.957-1,142	0.322			
Platelets	1,001	0.999-1,004	0.338			
Tumor size	1.036	0.987-1.088	0.150			
Number of tumors	1.434	1.037-1.984	<b>0.029</b>	1.494	1.071-2.084	<b>0.018</b>
AFP > 100 ng/mL and margins <1 cm			<b>&lt;0.001</b>	2.076	1.198-3.598	<b>0.009</b>

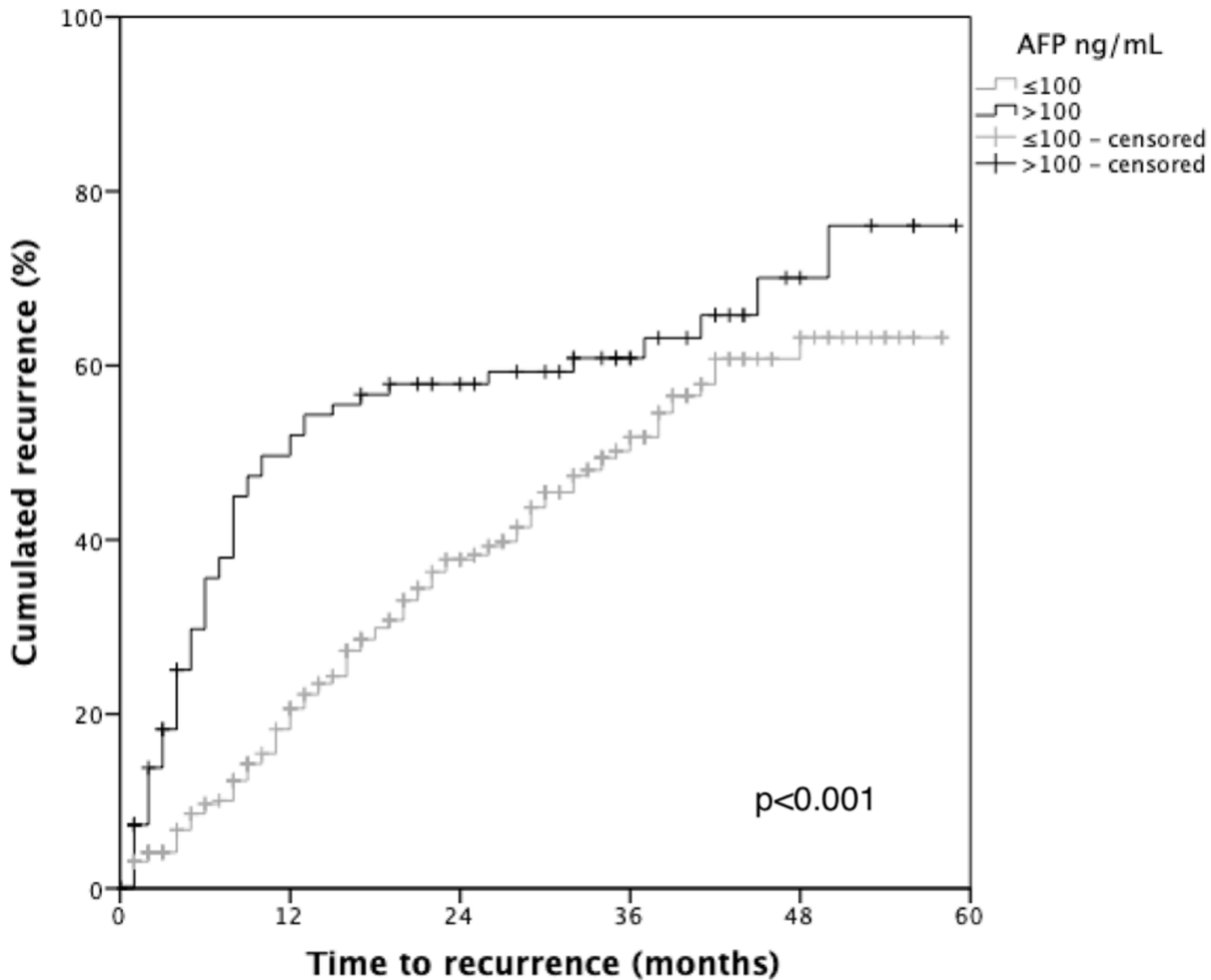
HR indicates Hazard ratio; CI, confidence interval; HCV, hepatitis C virus; HBV, hepatitis B virus; MELD, Model for End-stage Liver Disease(9, 10); AFP , alpha-fetoprotein

Figure 1



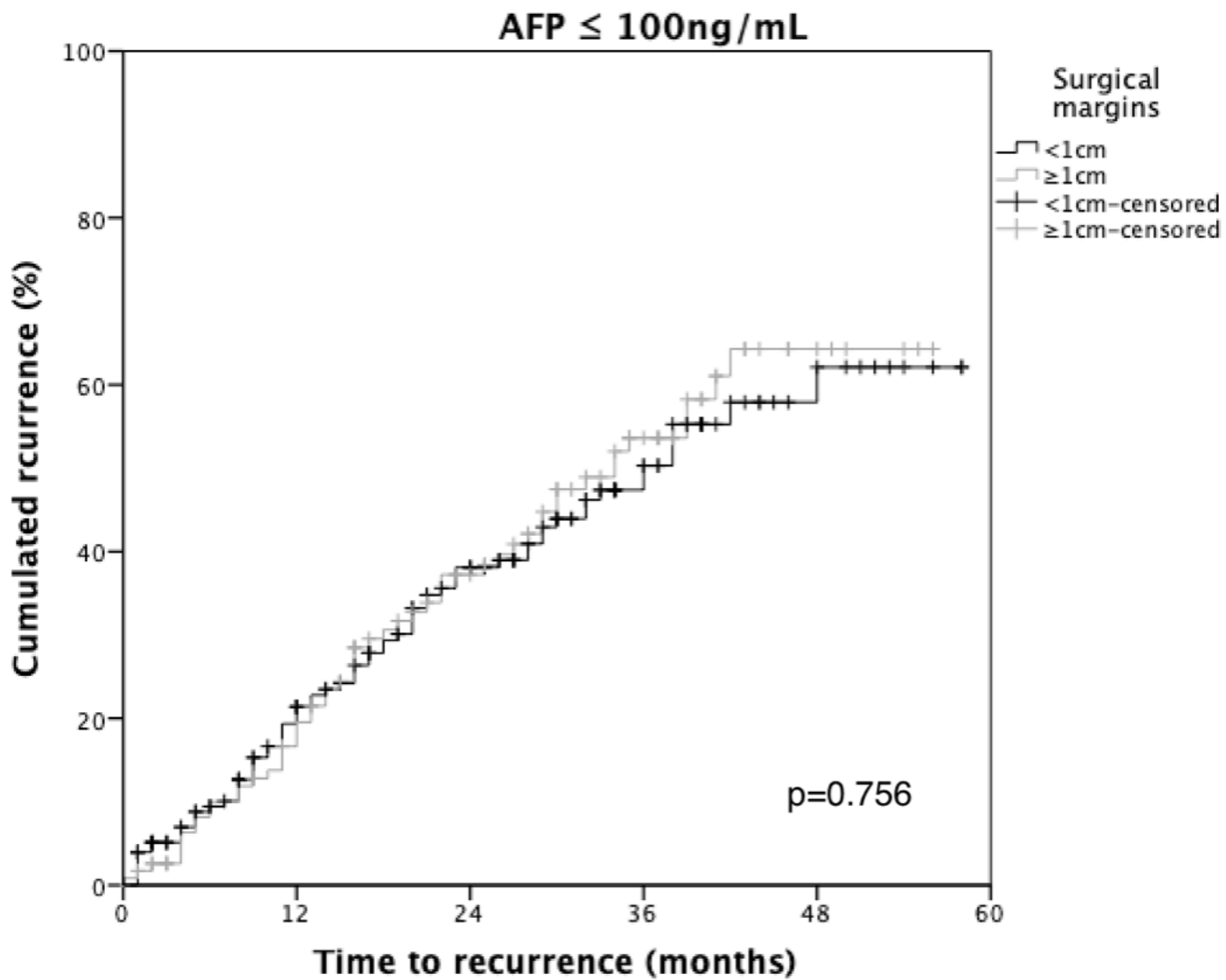
Time (Months)	0	12	24	36	48
< 1 cm	247	143	93	46	14
≥ 1 cm	150	105	68	35	8

Figure 2



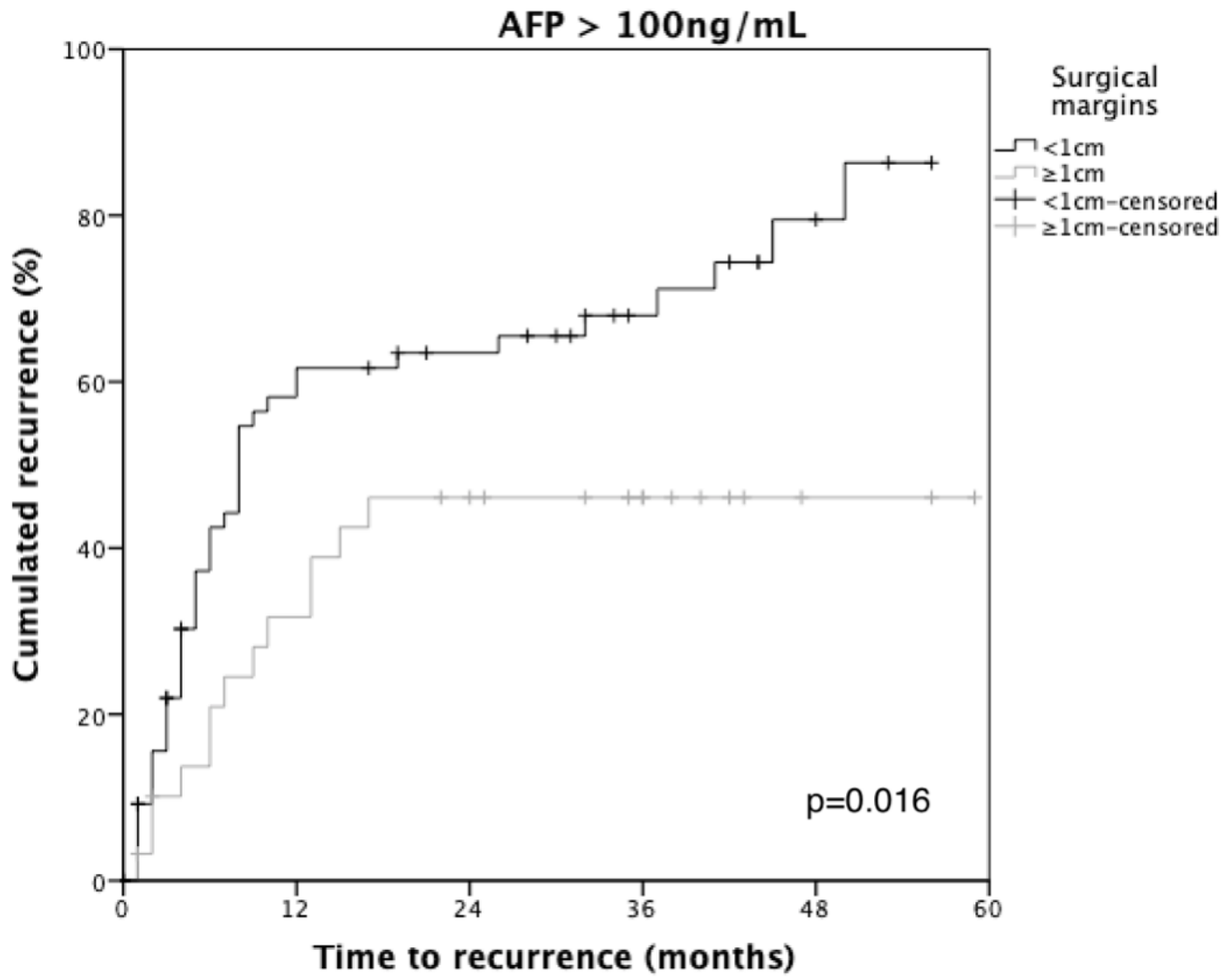
Time (Months)	0	12	24	36	48
AFP < 100 ng/mL	299	180	129	62	16
AFP ≥ 100 ng/mL	98	43	32	19	6

Figure 3a



Time (Months)	0	12	24	36	48
< 1 cm	180	119	75	36	10
≥ 1 cm	119	86	54	26	6

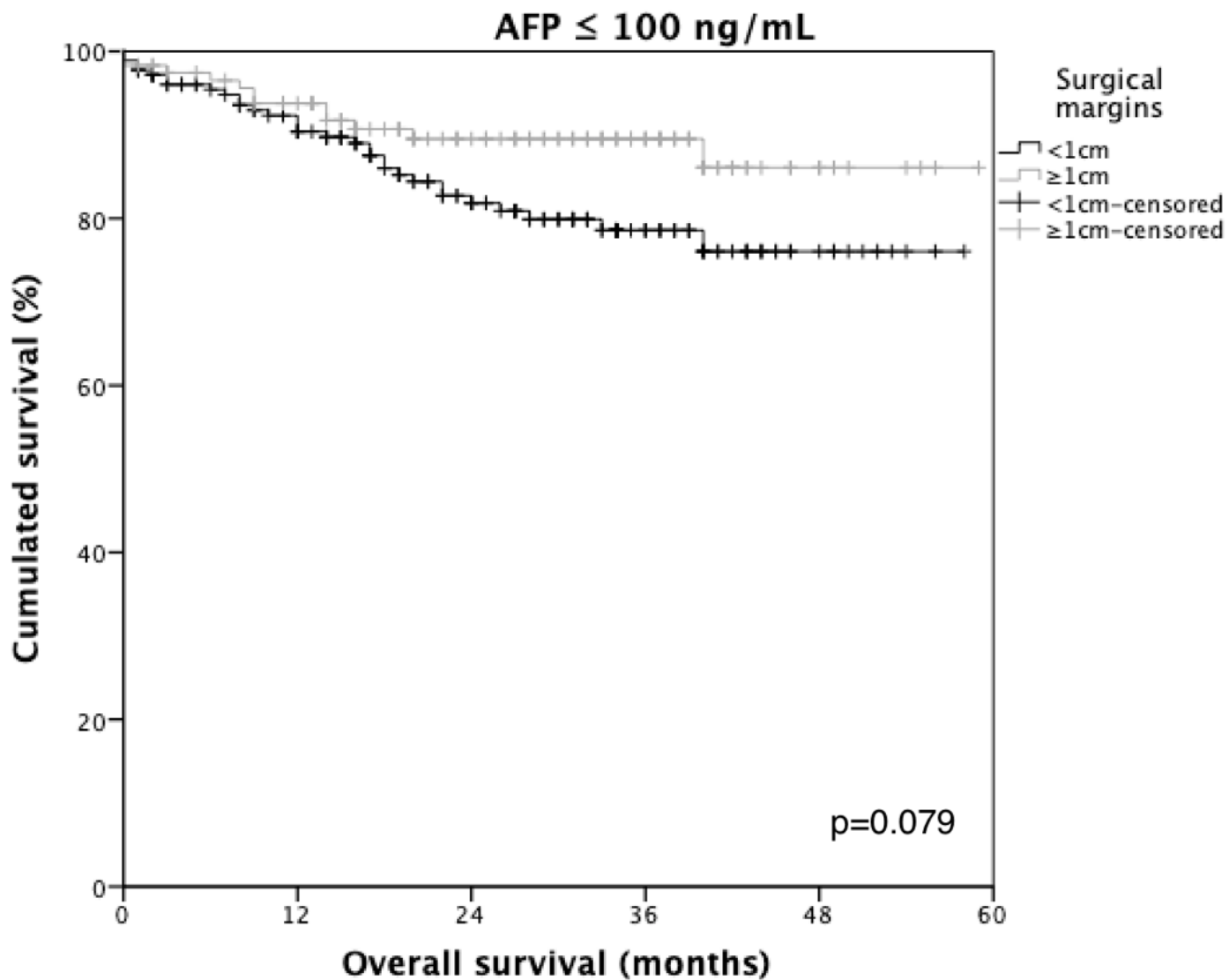
Figure 3b



<b>Time (Months)</b>	0	12	24	36	48
<b>&lt; 1 cm</b>	67	24	18	10	4
<b>≥ 1 cm</b>	31	19	14	9	2

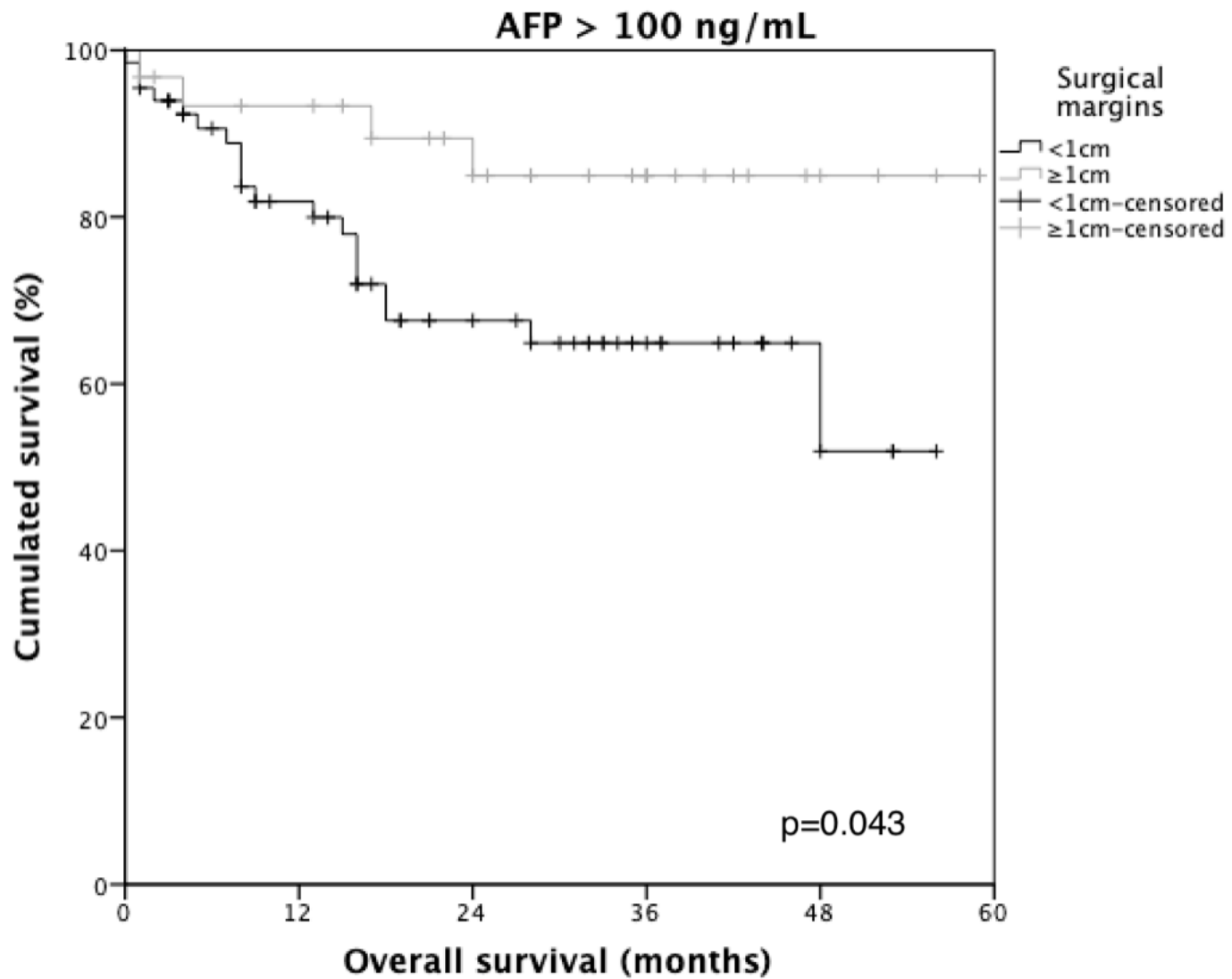


Figure 4a



<b>Time (Months)</b>	0	12	24	36	48
<b>&lt; 1 cm</b>	180	143	94	44	11
<b>≥ 1 cm</b>	119	98	67	39	8

Figure 4b



<b>Time (Months)</b>	0	12	24	36	48
<b>&lt; 1 cm</b>	67	43	27	14	5
<b>≥ 1 cm</b>	31	26	20	12	4