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Prediction of overall survival in patients with hepatocellular carcinoma treated with Y-90 radioembolization using imaging response criteria

Prognostic role of imaging after radio-embolization of hepatocellular carcinoma

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Abstract

Purpose: To evaluate the potential of imaging criteria in predicting overall survival of patients with hepatocellular carcinoma (HCC) after a first transcatheter arterial yttrium-90 radioembolization (TARE)

Materials and methods: From October 2013 to July 2017, 37 patients with HCC were retrospectively included. There were 34 men and 3 women with a mean age of 60.5 ± 10.2 (SD) years (range: 32.7 - 78.9 years). Twenty-five patients (68%) were Barcelona Clinic Liver Cancer (BCLC) C and 12 (32%) were BCLC B. Twenty-four primary index tumors (65%) were > 5 cm. Three radiologists evaluated tumor response on pre- and 4 – 7 months post-TARE magnetic resonance imaging or computed tomography examinations, using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, modified RECIST (mRECIST), European Association for Study of the Liver (EASL), volumetric RECIST (vRECIST), quantitative EASL (qEASL) and the Liver Imaging Reporting and Data System treatment response algorithm. Kaplan-Meier survival curves were used to compare responders and non-responders for each criterion. Univariate and multivariate Cox proportional hazard ratio (HR) analysis were used to identify covariates associated with overall survival. Fleiss kappa test was used to assess interobserver agreement.

Results: At multivariate analysis, RECIST 1.1 (HR: 0.26; 95% confidence interval [95% CI]: 0.09 – 0.75; $P= 0.01$), mRECIST (HR: 0.22; 95% CI: 0.08 – 0.59; $P= 0.003$), EASL (HR: 0.22; 95% CI: 0.07 – 0.63; $P= 0.005$), and qEASL (HR: 0.30; 95% CI: 0.12 – 0.80; $P= 0.02$) showed a significant difference in overall survival between responders and nonresponders. RECIST 1.1 had the highest interobserver reproducibility.

Conclusion: RECIST and mRECIST seem to be the best compromise between reproducibility and ability to predict overall survival in patients with HCC treated with TARE.

Keywords: Carcinoma, hepatocellular; Yttrium radioisotopes; Embolization, therapeutic; Response evaluation criteria in solid tumors; Survival analysis.

Abbreviations

2D: two-dimensional

3D: three-dimensional

AFP: α -fetoprotein

BCLC: Barcelona Clinic Liver Cancer

CE: contrast-enhanced

95% CI: 95% confidence interval

CR: complete response

CT: computed tomography

EASL: European Association for Study of the Liver

EPI: echo-planar imaging

FOV: field of view

FS: fat suppressed

HASTE: half-Fourier acquisition single-shot turbo spin-echo

HBV: hepatitis B virus infection

HCC: hepatocellular carcinoma

HCV: hepatitis C virus infection

HR: hazard ratio

LI-RADS: Liver Imaging Reporting and Data System

MELD: Model for End-Stage Liver Disease

MRI: magnetic resonance imaging

mRECIST: modified Response Evaluation Criteria in Solid Tumors

NASH: nonalcoholic steatohepatitis

No: number

NR: non-responder

OS: overall survival

PD: progression disease

PET: positron emission tomography

PR: partial response

Q1: first quartile

Q3: third quartile

qEASL: quantitative EASL

RECIST: Response Evaluation Criteria in Solid Tumors

SD: standard deviation

T1W: T1-weighted

T2W: T2-weighted

TACE: transcatheter arterial chemoembolization

TARE: transcatheter arterial yttrium-90 radioembolization

TRA: treatment response algorithm

TSE: turbo-spin echo

VIBE: volumetric interpolated breath-hold examination

vRECIST: volumetric RECIST

⁹⁰Y: yttrium-90

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide [1]. Among the current locoregional therapies used in patients not eligible for surgery, transcatheter arterial yttrium-90 (⁹⁰Y) radioembolization (TARE) is effective and safe, and can even result in downstaging before liver transplantation [2,3,4].

Although imaging response after TARE for HCC can predict overall survival (OS) [5], there is a lack of consensual guidelines for evaluation modalities. The most common methods used are: Response Evaluation Criteria in Solid Tumors (RECIST) 1.1; modified RECIST (mRECIST); and the European Association for the Study of the Liver (EASL) criteria [5,6,7]. RECIST 1.1 considers the largest one-dimensional measurement of the tumor while mRECIST and EASL both focus on the enhancing tumor, representing the viable tumor, in one and two dimensions, respectively [5]. However, tumors may undergo heterogeneous changes and grow or shrink asymmetrically which would affect the reliability of these

methods [8]. The treatment response algorithm (TRA) proposed in the Liver Imaging Reporting and Data System (LI-RADS) version 2018 has also shown interesting results in predicting HCC overall survival after locoregional therapies [9,10,11].

Quantitative EASL (qEASL) was introduced for a three-dimensional (3D) assessment of the enhancing tumor volume on arterial phase [12]. qEASL shows high degrees of correlation with HCC pathological necrosis after transarterial chemoembolization (TACE) [13]. Moreover, qEASL may predict survival better than RECIST, mRECIST and EASL in HCC patients treated with TACE [14,15]. However, its application in HCC patients after TARE remains unknown.

The purpose of this study was to evaluate the potential of imaging criteria in predicting OS in patients with HCC after a first TARE session.

Materials and methods

This was a retrospective single-institution study. Institutional review board approval was obtained (number: CRM-2003-076). Alive patients were informed, and their non-opposition was collected. As for deceased patients, non-opposition of a legal representative was not needed in accordance with French legislation.

Patient selection

A multidisciplinary liver tumor board determined the indication for TARE treatment. Inclusion criteria were: *i*), age ≥ 18 years; *ii*), Child-Pugh liver function class A or B score of 7 or lower; *iii*), HCC diagnosis made histologically or with contrast-enhanced (CE) computed tomography (CT) or magnetic resonance imaging (MRI) according to the EASL or American Association for the Study of Liver Diseases guidelines [3,16,17]; *iv*), Barcelona Clinic Liver Cancer (BCLC) stage B with contraindication or unsuccessful TACE, or BCLC stage C with portal vein thrombosis; and *v*), available CE magnetic resonance (MR) or CT images performed 4–6 weeks before TARE and 4–7 months after TARE. To reflect clinical practice in real life, patients with ill-defined tumors, portal thrombosis or previous treatments were not excluded. A flowchart of patient selection is shown in Figure 1.

Patients with missing imaging before TARE (done in another center), followed in another center, or missing clinical or biological follow-up were excluded. Clinical, imaging and laboratory values were evaluated before and after TARE. The observation period ended in June 30, 2018. The study endpoint was OS.

TARE

A multidisciplinary tumor board composed of an interventional radiologist, a nuclear medicine physician and a medical physicist performed the TARE procedures, using a previously described technique [18,19]. Patients underwent pre-intervention mapping angiography using cone beam CT and 99mTc-macroaggregated albumin single photon emission computed tomography [20] . Briefly, TARE was performed using glass-based microspheres (Thera-Sphere®; Biocompatibles UK Ltd, BTG International group company) or resin-based microspheres (SIR-Spheres®; Sirtex Medical,) injected through an intra-arterial microcatheter directly into the tumor. Treatment was as selective as technically and anatomically possible. For patients with bilobar disease, each hemiliver was treated separately within a month to avoid hepatotoxicity [18]. The median injected activity was 1.75 Giga Becquerel (GBq) (mean: 2.16 ± 0.90 [SD] GBq; range: 1.00 – 3.74 GBq; Q1 – Q3: 1.54 – 3.10 GBq). Positron emission tomography (PET)/CT performed immediately after TARE confirmed technical success with delivery of the whole ^{90}Y dose to the tumor and perfused adjacent parenchyma and no extra-hepatic fixation.

Imaging techniques

All the patients underwent a standardized liver imaging protocol including CE MRI or CT when MRI was contraindicated.

MRI

MRI was performed with a 1.5T (Magnetom Avanto®, Siemens Healthineers) or a 3T MR scanner (Magnetom Skyra®, Siemens Healthineers). The protocol included at least axial T1-weighted imaging (in-phase and out-of-phase), half Fourier acquisition single-shot turbo-spin echo, axial turbo spin-echo T2-weighted imaging with fat suppression, diffusion-weighted imaging with 3b values (50, 400 and 800 s/mm²) and breath-hold unenhanced and CE T1-weighted 3D fat-suppressed spoiled gradient echo-imaging in the hepatic arterial (45 s), portal venous (70 s), and delayed (180 s) phases. Gadoterate meglumine (Dotarem®; Guerbet) was administered at a dose of 0.1 mmol/kg, followed by 20 mL saline flush (2.5 mL/second) with a power injector. Detailed MRI protocols are provided in Table 1.

CT

CT imaging was performed with a multi-detector CT scanner (Discovery® HD 750 or

Revolution® CT, GE Healthcare, Milwaukee, WI, USA). The scanner parameters were: 120 kVp, 350 mA; 1.5 mm thick section, a 300 - 400 mm field of view (matrix size 512 × 512). The protocol included unenhanced, arterial, portal venous and delayed phases after injection of non-ionic contrast material (Iomeron® 350, Bracco) at a rate of 4 mL/s and a concentration of 1.5 mL/kg. Bolus tracking software (Smartprep®, GE Healthcare) was used and late arterial and portal venous phases were acquired respectively 20 s after the attenuation increase in the abdominal aorta reached the predefined threshold of 80 Hounsfield Units and 40 s thereafter. The delayed venous phase was acquired at 3 min delay.

2D tumor response assessment

Three radiologists (one junior: M.G., and two seniors: V.T. and R.K., with 4, 8 and 11 years of experience, respectively) independently compared pre-TARE and 4 –7 months post-TARE MR or CT images, using RECIST 1.1, mRECIST, EASL and LI-RADS TRA methods. They were all blinded to patient outcome. Two of them (M.G. and R.K.) did not perform any of the TARE procedures.

The primary index tumor was defined as the largest target tumor. Up to two primary target lesions (including the primary index tumor) per patient were analyzed, as well as all non-target lesions defined as the remaining tumor burden [6,17,21,22]. Overall tumor response was based on target lesions response, non-target tumor response and the advent of new lesion [6,7,17,21,22].

For RECIST 1.1, mRECIST and EASL, patients with overall complete response (CR) or partial response (PR) were categorized as responders; those with stable disease or progressive disease (PD) were categorized as nonresponders (NR) [23]. Patients with stable disease were classified as NR because tumors without any enhancement or size decrease could merely be slowly growing tumors rather than indicating treatment response. As for LI-RADS TRA, patients categorized as viable or equivocal were classified as nonresponders, and those categorized as non-viable were classified as responders.

3D tumor response assessment

The three observers independently performed 3D quantitative tumor assessment using a semiautomatic 3D software prototype (Medisys®; Philips Research) as described in detail in previous studies [14,15]. Briefly, a 3D semiautomatic tumor segmentation was performed by each of the three readers on the arterial phase CT or MR images before and after TARE. From

the tumor segmentation, the whole tumor volume and the enhancing portion of tumor volume (cm^3) could be obtained. To measure the enhancing volume, unenhanced CT or MR was subtracted to the arterial phase CT or MR in order to remove any background attenuation. The 3D tumor segmentation mask was then transposed onto this subtracted CT or MR. The enhancing tumor volume was obtained as follows: a region of interest formed by 1 cm^3 was placed by the radiologist in the normal appearing liver parenchyma as a reference for normalization to calculate the relative enhancement within the tumor [13,24]. An example of the segmentation outline and 3D rendering produced is shown in Figure 2. qEASL and vRECIST methods were calculated as in Duran et al. study: when all target lesions disappeared, the patient was classified as a CR [25]. A decrease $\geq 65\%$ in volume of the target lesions was noted as PR, and PD was defined as an increase $\geq 73\%$ of the volume of the target lesions. All other situations were considered as stable disease.

Statistical analysis

The Shapiro-Wilk test was used to determine if the measurements were normally distributed. Since all variables were not normally distributed, quantitative variables were expressed as medians, means, SD, ranges, Q1 and Q3. Qualitative variables were all expressed as raw numbers, proportions and percentages. The Wilcoxon signed-rank test was used to assess whether modification of index lesion size was statistically significant.

Statistical tests used for comparison were respectively: Student t-test for age, Wilcoxon test for α -Fetoprotein and tumors diameter, Fisher exact test for sex, method of diagnosis, etiology of hepatopathy, cirrhosis, Child-Pugh class, BCLC stage, total number of TARE procedures, portal vein thrombosis and ill-defined tumor borders.

The proportional hazard assumption was checked by plotting the Schoenfeld residuals. Goodness-of-fit was assessed by plotting the Cox-Snell residuals. Discriminant ability was assessed using Harrell's C index.

Univariate and multivariate analyses were conducted to identify factors associated with survival. Survival analysis was performed with the Kaplan–Meier method and the log-rank test. Cox proportional hazards model was used to examine risk factors associated with survival. Variables with a P value ≤ 0.10 at univariate analysis were entered into the multivariate model. Univariate Cox regression evaluated the association of survival with each of the following baseline factors: age, α -fetoprotein level before TARE, Child-Pugh stage before TARE, BCLC stage before TARE, Model For End-Stage Liver Disease (MELD) score

before TARE, presence of cirrhosis, tumor size, portal vein thrombosis, a past history of curative treatments, hepatic surgery after TARE [26]. Sex was not considered because of the too small number of female patients in our study. Univariate Cox regression was also performed for each radiologic measurement: RECIST, mRECIST, EASL, vRECIST, qEASL and LI-RADS. Radiologic measurements used in the survival analysis were those obtained by the most experienced radiologist (V.T.). Each factor with a P value ≤ 0.10 in the univariate analysis was then included in the multivariate Cox regression analysis to calculate adjusted hazard ratio (HR) for each radiologic measurement [27].

The Fleiss Kappa test was used to evaluate the agreement on the overall response which was calculated by taking into account responders versus nonresponders [28]. The strength of agreement based on kappa values was interpreted as follows: 0.01 – 0.20, slight agreement; 0.21 – 0.40, fair agreement; 0.41 – 0.60, moderate agreement; 0.61 – 0.80, substantial agreement; 0.81 – 0.99, almost perfect agreement [29]. A difference with a two-tailed P value < 0.05 was considered to indicate significance. All statistical analyses were performed using R Studio (R studio®, version 4.0.2) except Fleiss Kappa which was calculated using the SPSS statistical software program (SPSS®, version 27.0; SPSS Chicago, Ill).

Results

Study group characteristics

From October 1, 2013 to July 31, 2017, of the 84 patients who underwent TARE for liver cancer, 70 had HCC. Thirty-seven patients underwent a first TARE and had available MR or CT imaging performed 4 – 6 weeks before TARE and 4 – 7 months after TARE and were enrolled in the study. There were 34 (34/37, 92%) men and 3 (3/37, 8%) women with a mean age of 60.5 ± 10.2 [SD] years (range: 32.7 – 78.9 years). Patient characteristics are shown in Table 2. Twenty-four primary index tumors (24/37, 65%) were larger than 5 cm. Twenty-three patients (23/37, 62%) underwent only one TARE. Comparison between analyzed and excluded patient characteristics is shown in Table 3.

MR and CT imaging analysis

The median time from the TARE procedure to CE MRI or CT used for imaging evaluation was 175 days (mean, 178.5 ± 18.4 [SD] days; range: 155 – 237 days, Q1-Q3: 164 –

189 days). After TARE, the median tumor diameter (RECIST 1.1) decreased from 5.7 cm (mean: 6.2 ± 3.9 [SD] cm, range: 1 – 17 cm; Q1 – Q3: 4.1 – 7.3 cm) to 4.5 cm (mean: 5 ± 3.4 [SD]; range: 0 – 13 cm; Q1 – Q3: 2.7 – 6.6 cm) ($P = 0.23$) and the median tumor enhancing lengths (mRECIST) decreased from 5 cm (mean: 6 ± 3.9 [SD] cm; range: 1 – 17 cm; Q1 – Q3: 4 – 6.5 cm) to 0 cm (mean: 2.7 ± 4 [SD] cm; range: 0 – 13 cm; Q1 – Q3: 0 – 4.9 cm) ($P = 0.02$). The median area of tumor enhancement (EASL) decreased from 18.9 cm² (mean: 31 ± 38.8 [SD] cm², range: 0.8 – 170 cm²; Q1-Q3: 9.2 – 31 cm²) to 0 cm² (mean: 13.3 ± 27 [SD] cm²; range: 0 – 138 cm²; Q1 – Q3: 0 – 18.5 cm²) ($P < 0.01$). The median tumor volume (vRECIST) decreased from 63 cm³ (mean: 201.5 ± 402 [SD] cm³; range: 0.41 – 1925 cm³, Q1 – Q3: 36.5 – 140 cm³) to 28.5 cm³ (mean: 117.5 ± 200 [SD] cm³; range: 0 – 867 cm³; Q1 – Q3: 7.8 – 110 cm³) ($P = 0.02$). The median volume of enhancing tumor (qEASL) decreased from 36.9 cm³ (mean: 63 ± 92.7 [SD]; range: 0.1 – 508 cm³; Q1-Q3: 12.6 – 78 cm³) to 6.03 cm³ (mean: 43.2 ± 82.1 [SD] cm³; range: 0 – 314 cm³; Q1-Q3: 0.3 – 22.3) ($P < 0.01$).

Survival analysis

During the observation period, 20 (20/37, 54%) patients died, and 11 (11/37, 30%) patients had hepatic surgery after TARE: 5 patients (5/37, 14%) had a hepatectomy and 6 (6/37, 16%) patients had a liver transplantation. The median OS of the entire patient population was 12.2 months (mean: 14.6 ± 10.6 [SD] months; range: 5.4 – 52 months; Q1 – Q3: 6.6 – 18.2 months). Results of univariate and multivariate analyses are shown in Tables 4 and 5, respectively. Among the clinical or biological criteria tested, treatment with hepatic surgery after TARE (HR: 0.25; 95% CI: 0.07 – 0.84; $P = 0.03$) showed a P value $\leq .10$ at univariate analysis and was included in the multivariate analysis. All measurements obtained with RECIST 1.1, mRECIST and EASL methods showed a significant difference in survival between responders and nonresponders for univariate and multivariate analyses (Tables 4 and 5; Figure 3). qEASL also revealed a significant difference in both univariate and multivariate analysis (Tables 4 and 5; Figure 4). vRECIST showed a significant difference in univariate analysis (HR: 0.29; 95% CI: 0.10 – 0.87; $P = 0.03$) but not in multivariate analysis (HR: 0.38; CI95: 0.12 – 1.17; $P = 0.09$). LI-RADS TRA (HR: 0.46; 95% CI: 0.17 – 1.24; $P = 0.13$) did not show a significant difference at univariate analysis.

All multivariate models had a good calibration (Figure 5). The discriminating capability of all models was good, with the highest Harrell's C index for RECIST and mRECIST models, as shown in Table 5.

Interobserver reproducibility

The overall response concordance between the three operators was substantial for RECIST 1.1 ($\kappa=0.77$; 95% CI: 0.58 – 0.96; $P < 0.01$) and EASL ($\kappa=0.63$; 95% CI: 0.45 – 0.83; $P < 0.01$), moderate for mRECIST ($\kappa=0.57$; 95% CI: 0.38 – 0.75; $P < 0.01$), vRECIST ($\kappa=0.46$; 95% CI: 0.28 – 0.65; $P < 0.01$), qEASL ($\kappa=0.42$; 95% CI: 0.24 – 0.61; $P < 0.01$), and LI-RADS TRA ($\kappa=0.46$; 95% CI: 0.29 – 0.66; $P < 0.01$) (Table 6).

Discussion

The main finding of this study is that RECIST and mRECIST and 2D EASL methods as well as 3D qEASL method, are valid independent response biomarkers that predict OS after TARE in patients with HCC.

Survival in patients with HCC depends not only on malignancy but also on underlying cirrhosis [17]. These patients usually have overlapping treatments and large studies are required to evaluate benefits and secondary effects of a single treatment. Assessing tumor response on post-treatment imaging is a key in therapeutic management. Thus, the aim of this study was to evaluate the performance of one-dimensional, 2D and 3D methods as surrogate endpoints to predict OS after a first TARE procedure in patients with HCC.

Difficulties in evaluating HCC response are well known [30], and 3D quantitative imaging has shown promising results in such patients [14]. Similar results have also been observed in liver metastatic disease; the same 3D methods are more accurate in predicting survival than one-dimensional and 2D methods [31]. However, such methodologies have not been validated in patients treated with HCC with TARE. This study evaluated 3D-based methods after TARE in patients with HCC and showed encouraging results in OS prediction with qEASL method. RECIST 1.1, mRECIST and EASL methods showed statistically significant differences between responders and nonresponders, confirming previously published studies [5].

The 3D quantitative methods used in this study have several methodologic strengths: they have been studied for CT and MRI; they have been validated in a previous radiologic-pathologic study; they are time efficient; and they provide precise volumetric tumor assessment [13,24,32]. These volumetric datasets are also helpful to guide the interventional radiologist during the procedure as they show the viable tumor and its feeding vessels [33].

Moreover, volumetric tumor assessment helps calculate the dose delivered to the tumor, which is an independent factor associated with tumor control and OS [34].

All the methods showed moderate interobserver agreement, except RECIST 1.1 and EASL which showed substantial agreement. Similar results for mRECIST have been reported in previous studies with low reproducibility in HCC lesions of heterogeneous enhancement [8]. In this study, some of the tumors analyzed were heterogenous, and the three readers did not have the same experience. Furthermore, some of the included patients had ill-defined tumors so as to better reflect clinical practice. Finally, analysis was limited to responders versus nonresponders which is the most meaningful information for clinical management and treatment decision making.

vRECIST and qEASL did not show higher interobserver reproducibility than the other methods. This might be partially due to the cubic variation of any change in diameter and to the placement of the region of interest, which may vary with imaging artefacts or heterogeneities [35,36]. The reproducibility of the 3D methods is also affected by the semi-automatic segmentation which makes it possible for the radiologist to do manual adjustments, but also leads to poorer reproducibility, especially with infiltrative tumor patterns. Software instability could also be a factor of variability of the results.

This study had some limitations. First, the retrospective design of the study, the low number of patients and the short follow-up time constitute classic limitations. Second, patients who exhibited vascular invasion or those who had previous or secondary treatments were not excluded in order to reflect clinical practice. Indeed, even though portal invasion is a well-known prognostic factor in HCC patients, TARE has become, due to its minimally embolic nature, an increasingly common indication for the treatment of HCC with associated portal vein thrombosis [37,38,39,40]. Portal invasion was included in the univariate and multivariate analysis and was not related to poorer survival in this study population. Third, additional study endpoints, such as early response and time to progression, were not evaluated and could be studied in future works [41]. However, in this study, the main objective was to evaluate the predictive value of the one, two and three-dimensional methods on OS. Therefore, the 4 – 7 months follow-up was chosen by consensus as a reference, as the median time to response to RECIST after arterial locoregional therapies is 7.7 months [21,42].

In conclusion, this study validates RECIST, mRECIST, EASL and qEASL as independent response biomarkers that predict OS after TARE in patients with HCC. RECIST and mRECIST seem to be the best compromise between reproducibility and predictability of

OS in these patients, but more data are required to confirm these results and evaluate their role in assessing early response.

Author contributions

All authors attest that they meet the current International Committee of Medical Journal Editors (ICMJE) criteria for Authorship.

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Declarations of interest

The authors declare that they have no competing interest..

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Tables & Figure legends

Figure 1. Flowchart shows patient selection criteria. TARE= Transcatheter arterial yttrium-90 radioembolization; HCC= hepatocellular carcinoma.

Figure 2. Magnetic resonance imaging examination of a 67-year-old man with a single hepatocellular carcinoma. Tumor was segmented before (first row: A, C and E) and after (second row: B, D and F) transcatheter arterial yttrium-90 radioembolization (TARE). First and second columns represent respectively unenhanced (A and B) and arterial phase axial T1 weighted (T1W) MRI images (C and D) in the axial plane. Red outline shows tumor segmentation. A region of interest (in green) was placed by the radiologist in the normal appearing liver parenchyma. Third column shows the quantitative European Association for Study of the Liver tumor color map (E and F) obtained after subtraction of the first column image from the second one. The blue color represents no arterial enhancement and the red color represents maximum arterial enhancement. In this case, before first TARE, the primary index tumor volume was 163 cm³ (E), with an enhancing volume of 91 cm³ (56% of the total tumor volume). After TARE, the tumor volume was 22 cm³ (F), with an enhancing volume of 4 cm³ (3% of the total tumor volume). The patient was classified as a responder.

Figure 3. Kaplan-Meier curves of overall survival in responders and nonresponders according to: A) Response Evaluation Criteria in Solid Tumors (RECIST 1.1); B) modified RECIST (mRECIST); C) European Association for Study of the Liver (EASL). *P* values resulted from the log-rank analysis. RECIST 1.1, mRECIST, and EASL methods all showed a statistically significant difference between nonresponders and responders.

Figure 4. Kaplan-Meier curves of overall survival in responders and nonresponders according to A) volumetric Response Evaluation Criteria in Solid Tumors (vRECIST); B) quantitative European Association for Study of the Liver (qEASL); C) Liver Imaging Reporting and Data System (LI-RADS) treatment response algorithm. *P* values resulted from the log-rank analysis. Both vRECIST and qEASL showed a statistically significant difference between nonresponders and responders, whether LI-RADS did not.

Figure 5 A. Graph of Cox-Snell residuals for RECIST multivariate model. RECIST= Response Evaluation Criteria in Solid Tumors. B. Graph of Cox-Snell residuals for mRECIST multivariate model. mRECIST= modified Response Evaluation Criteria in Solid Tumors. C. Graph of Cox-Snell residuals for EASL multivariate model. EASL= European Association for Study of the Liver. D. Graph of Cox-Snell residuals for vRECIST multivariate model. vRECIST= volumetric Response Evaluation Criteria in Solid Tumors. E. Graph of Cox-Snell residuals for qEASL multivariate model. qEASL= quantitative European Association for Study of the Liver.

Table 1. Magnetic resonance imaging protocol.

Table 2. Baseline characteristics of 37 patients treated with transcatheter arterial yttrium-90 radioembolization.

Table 3. Comparison between included (n= 37) and excluded (n= 33) patients with hepatocellular carcinoma treated with transcatheter arterial yttrium-90 radioembolization.

Table 4. Results of univariate analysis in 37 patients with HCC treated with transcatheter arterial yttrium-90 radioembolization with 20 events.

Table 5. Results of multivariate analysis results (total number of patients = 37, total number of events = 20).

Table 6. Fleiss kappa values for overall response concordance.

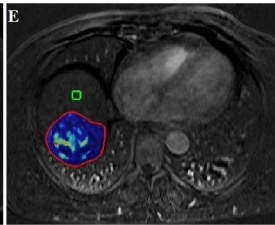
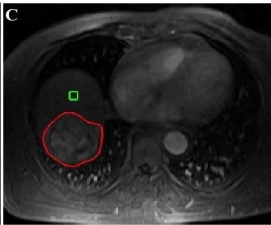
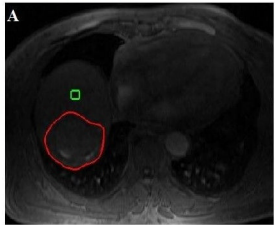
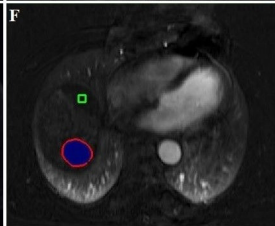
84 patients treated with TARE between October 2013 and July 2017

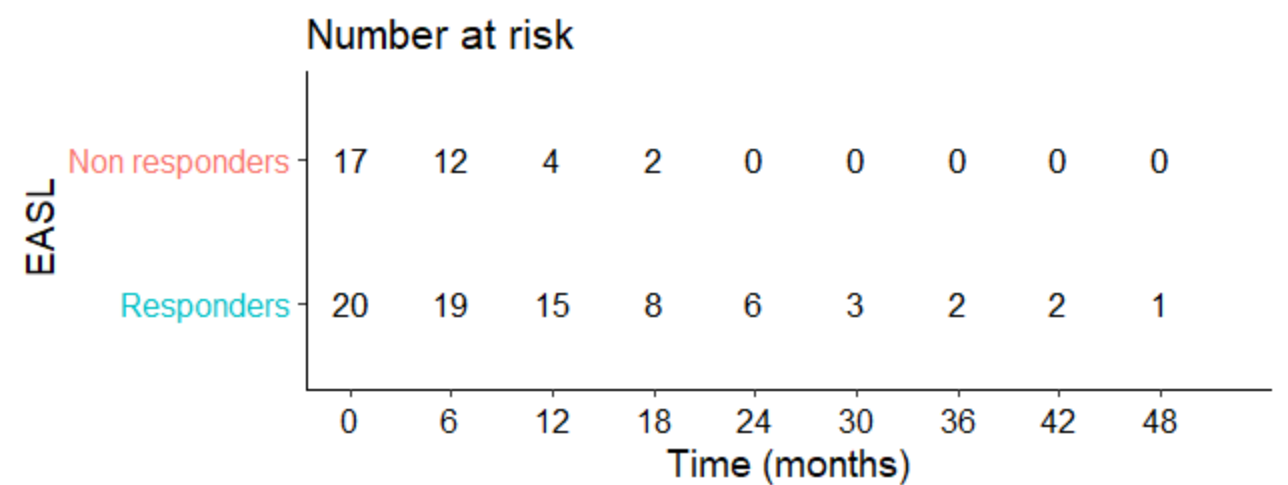
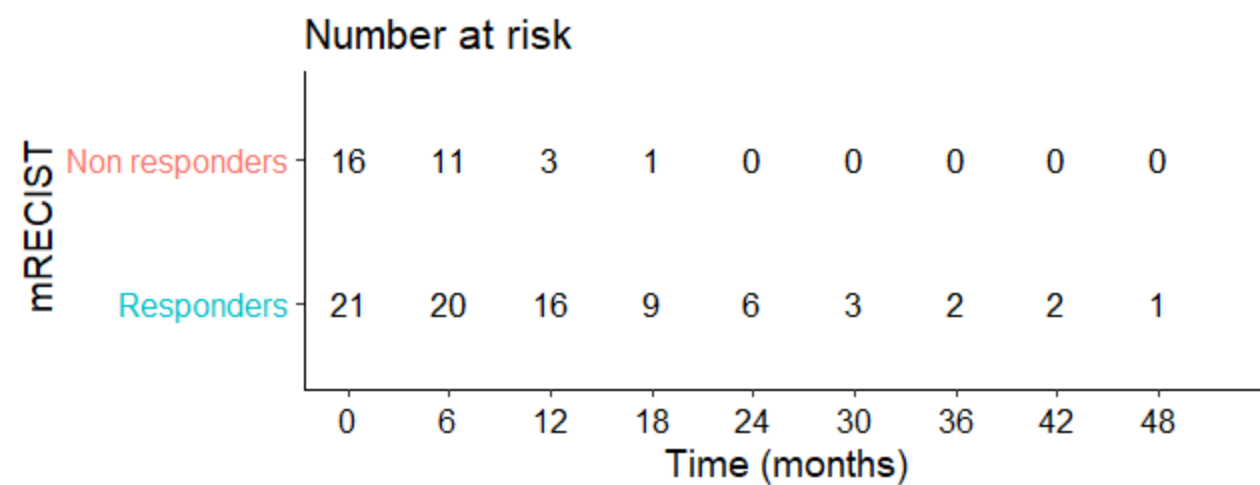
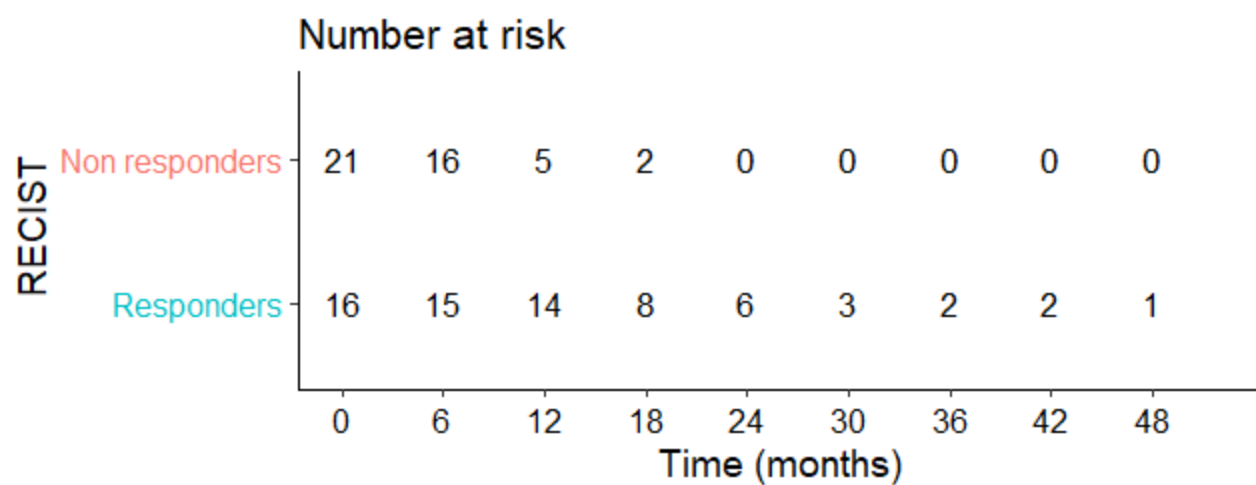
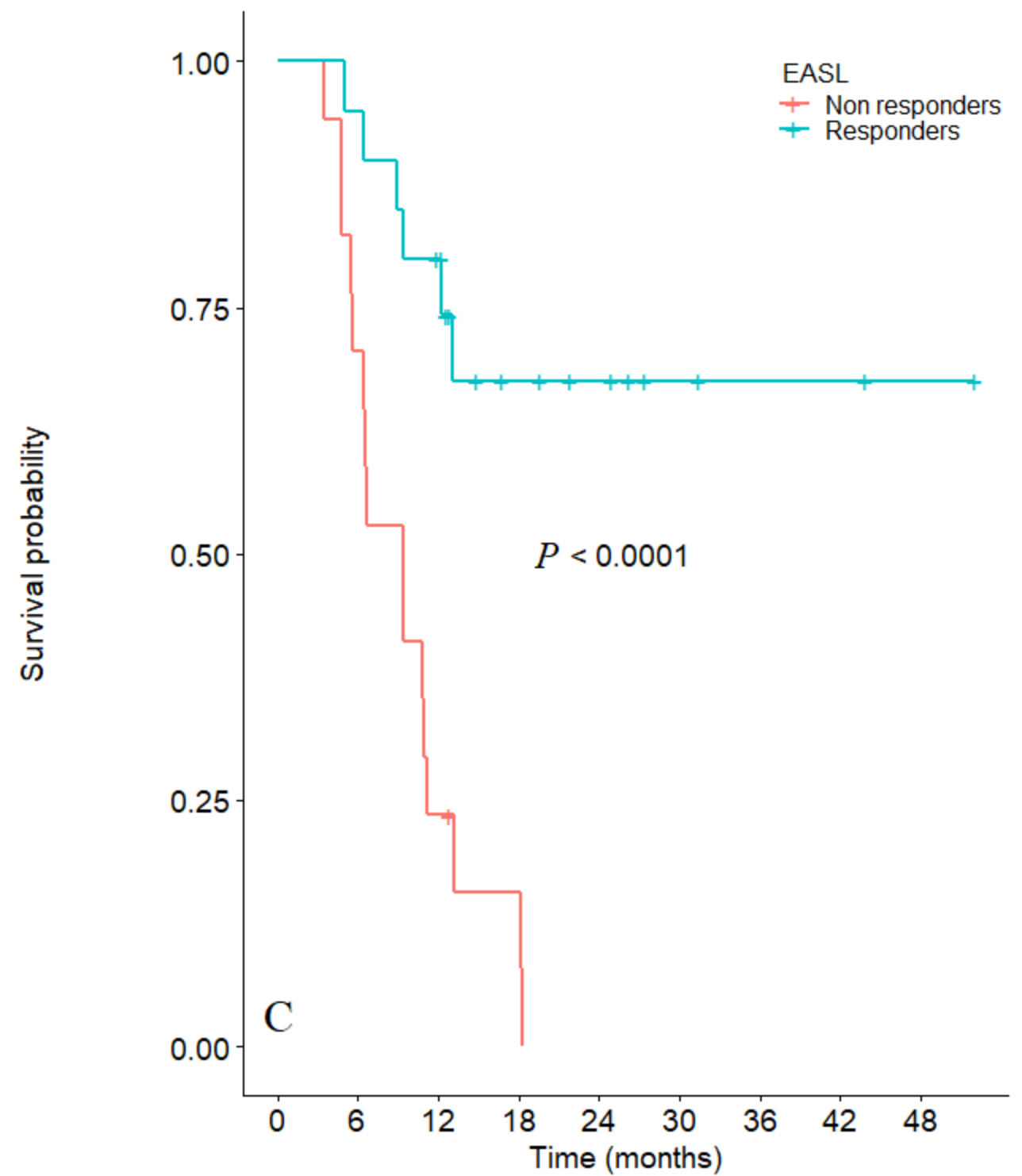
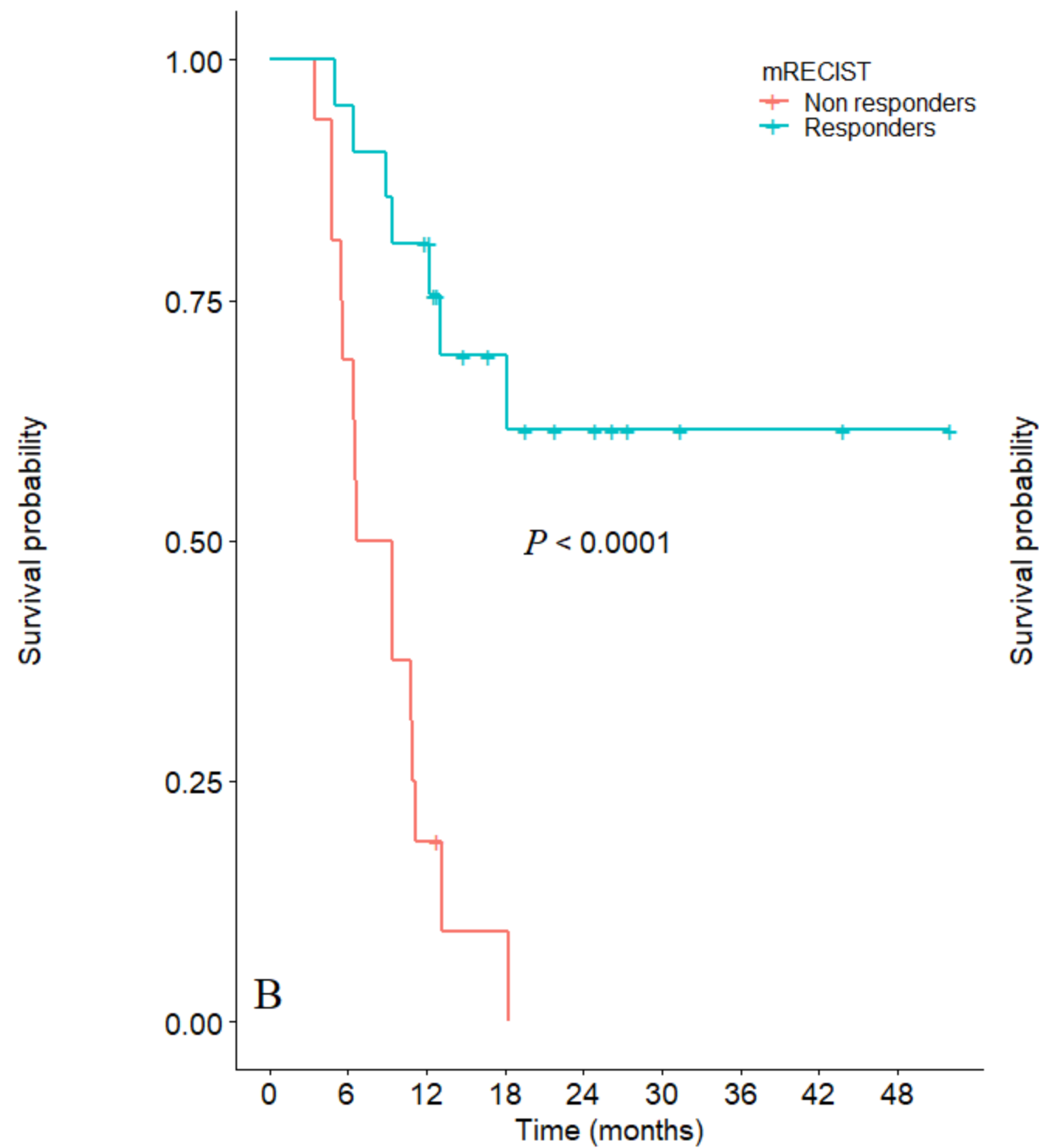
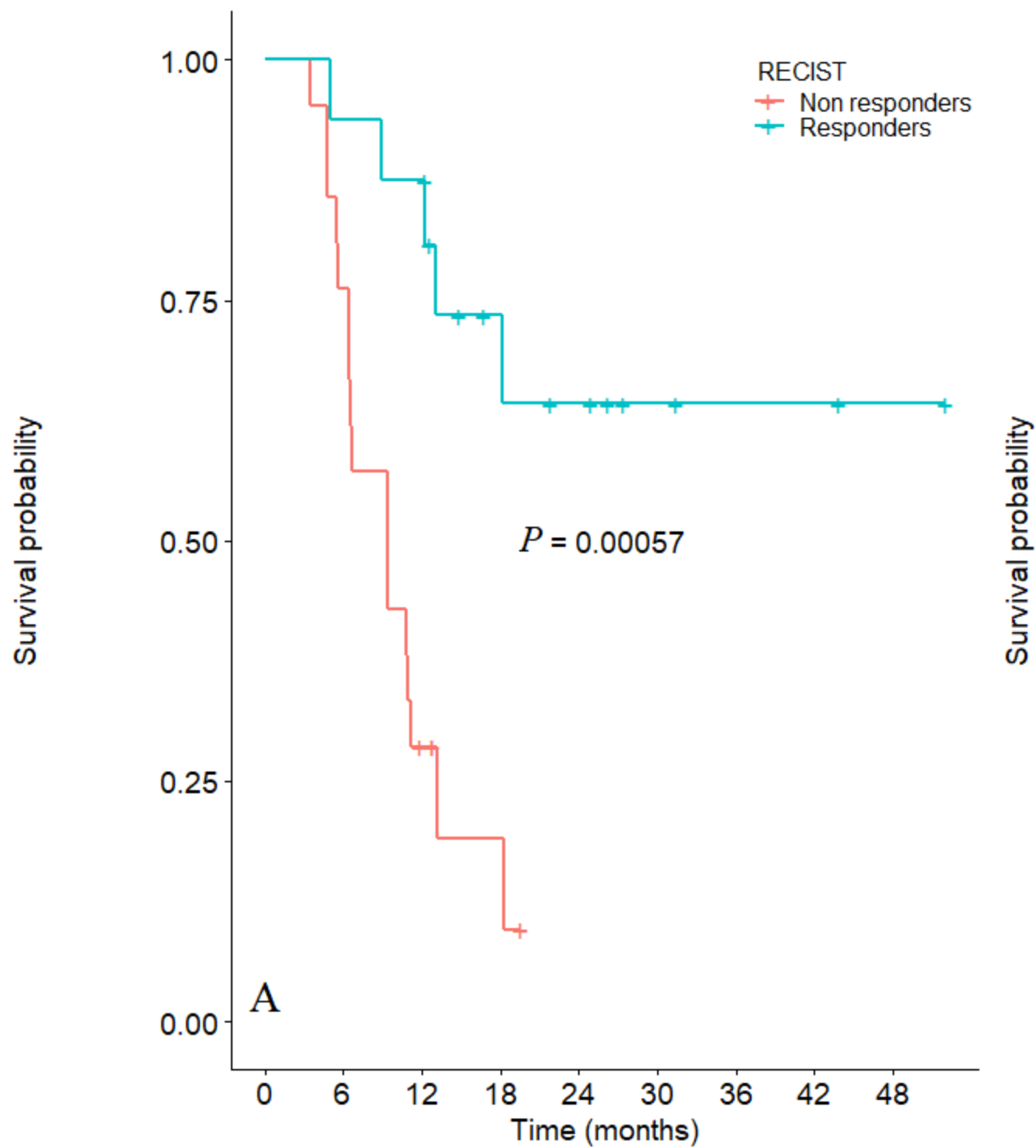
Excluded patients (n = 14; 17%)
No HCC

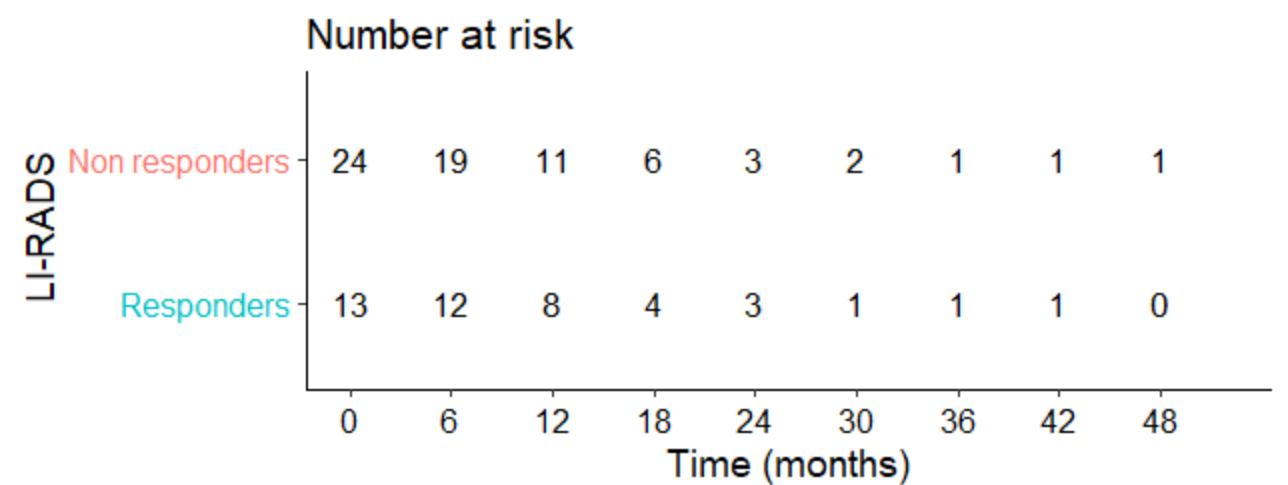
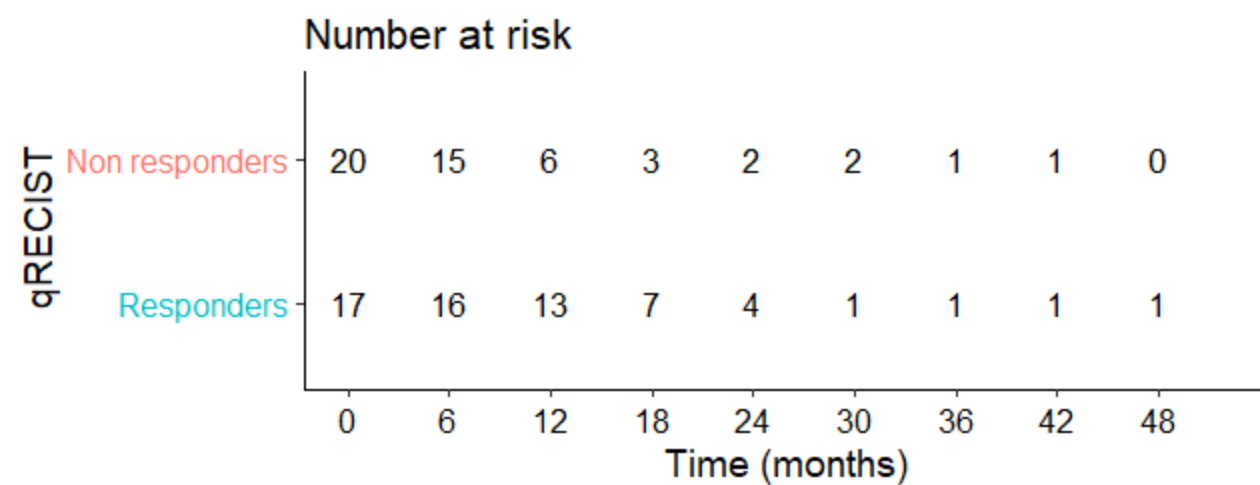
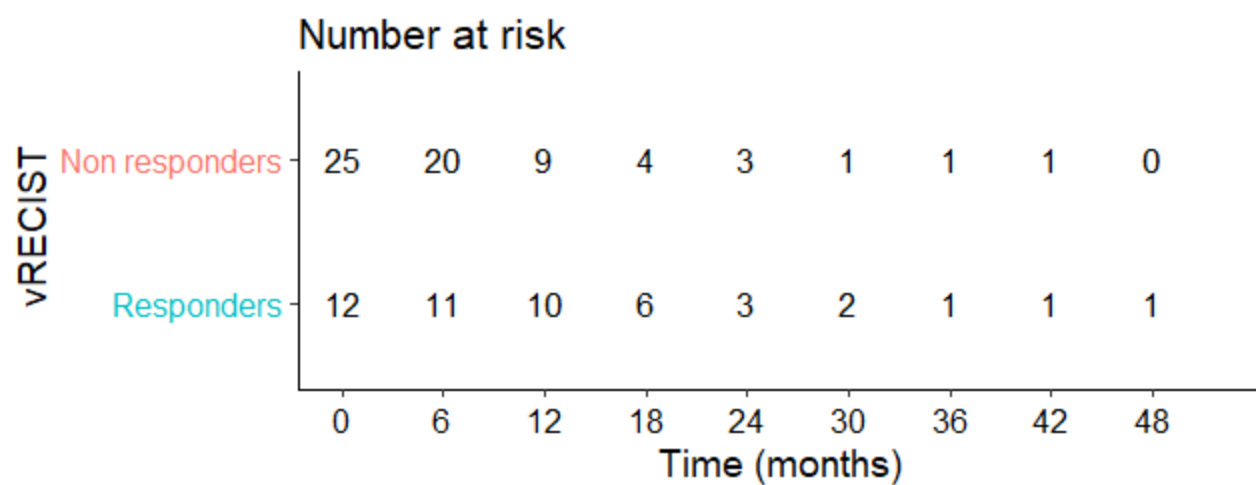
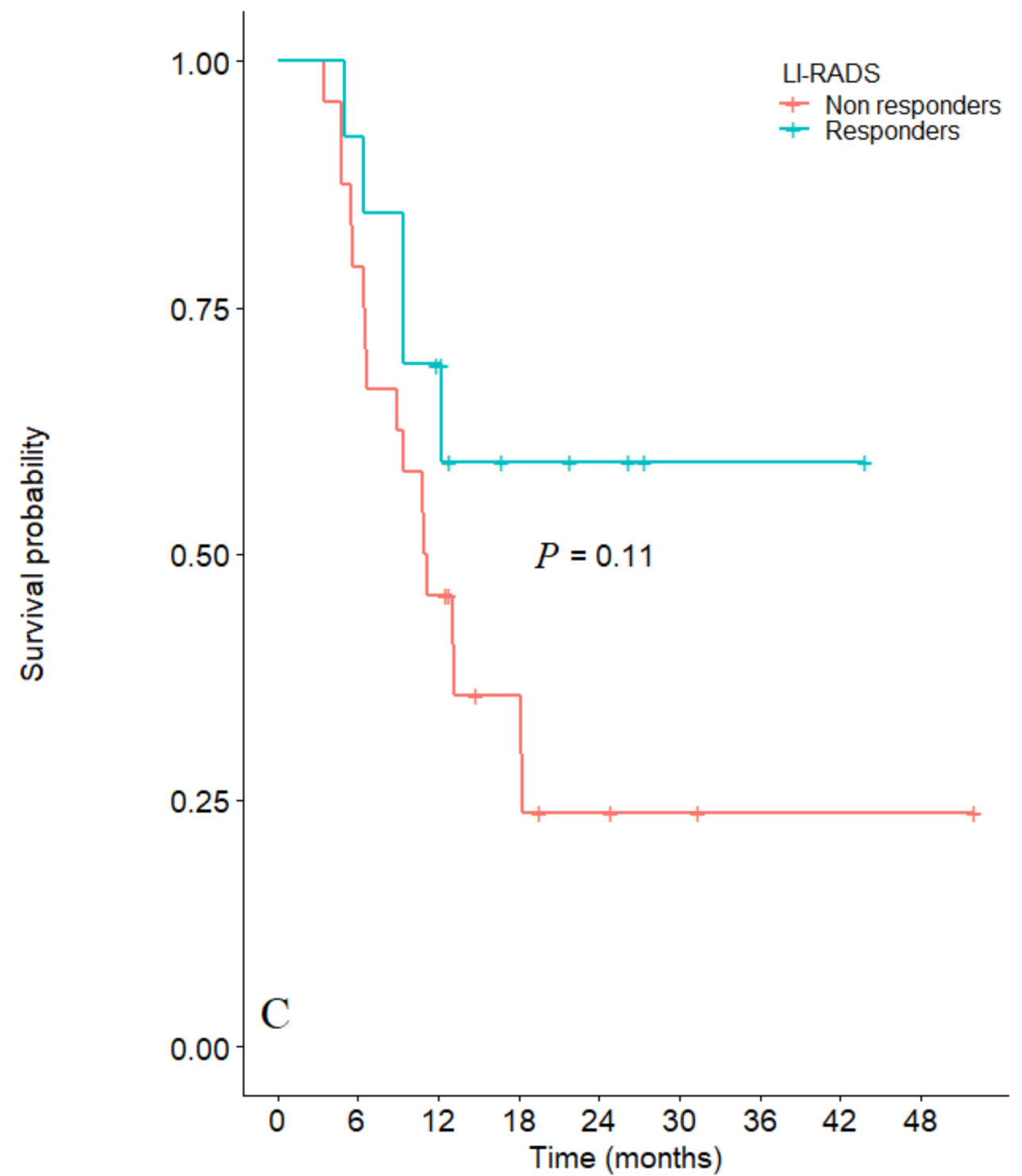
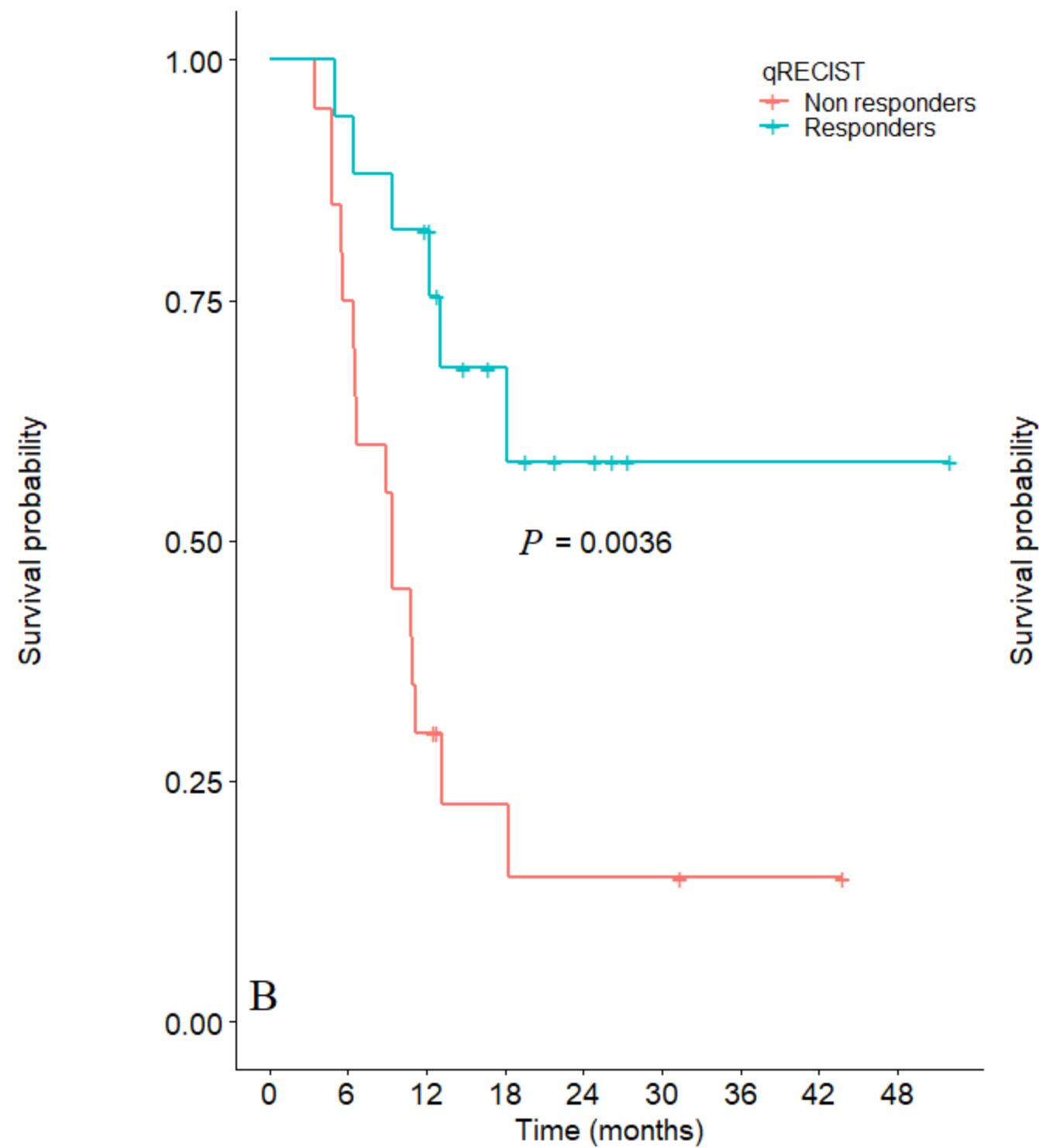
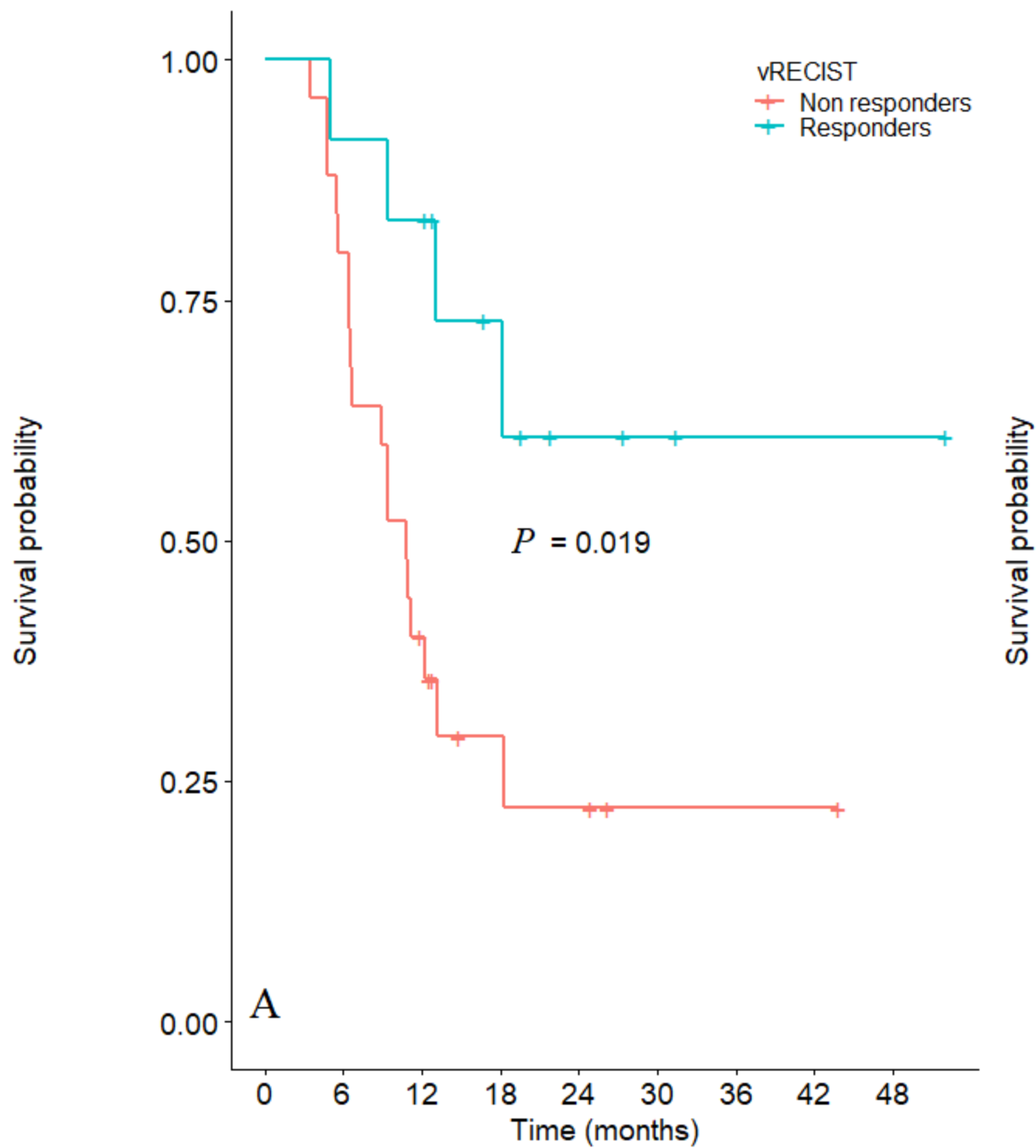
70 eligible patients with HCC treated with TARE

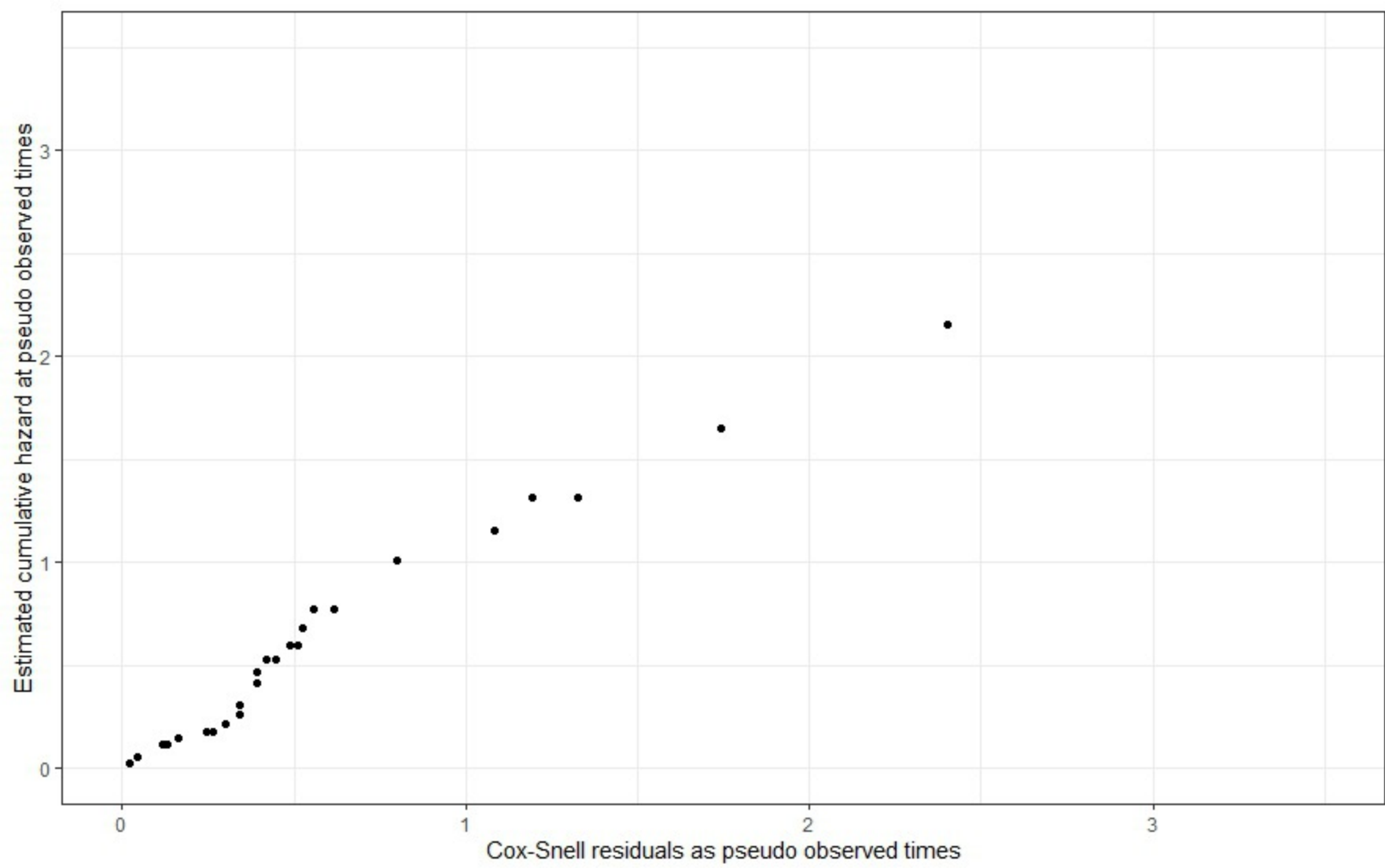
Excluded patients (n = 33; 47%)
Imaging before TARE in
another center (n = 13)
Follow-up in another center
(n = 10)
Missing clinical or biological
follow-up (n = 10)

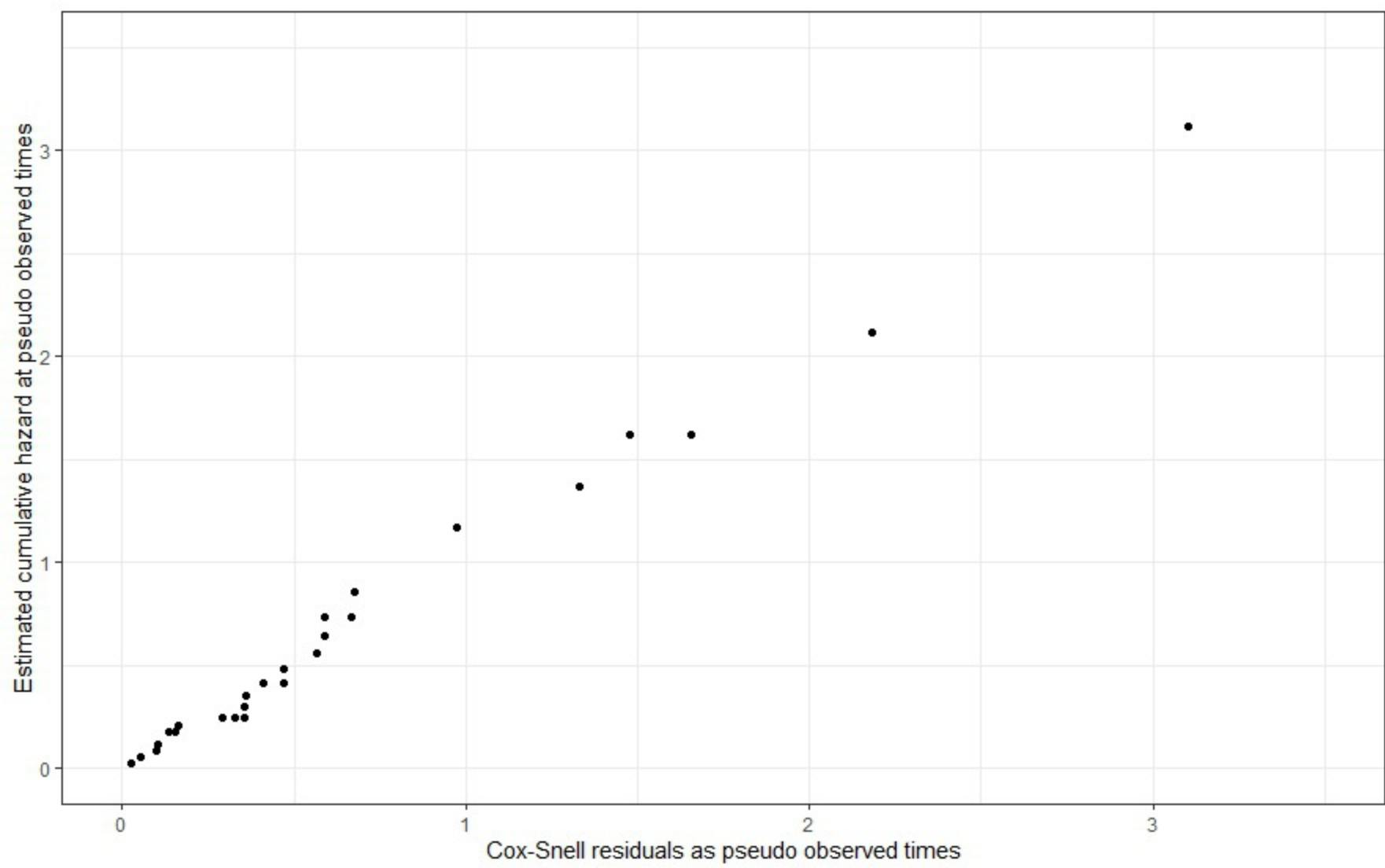
37 included patients

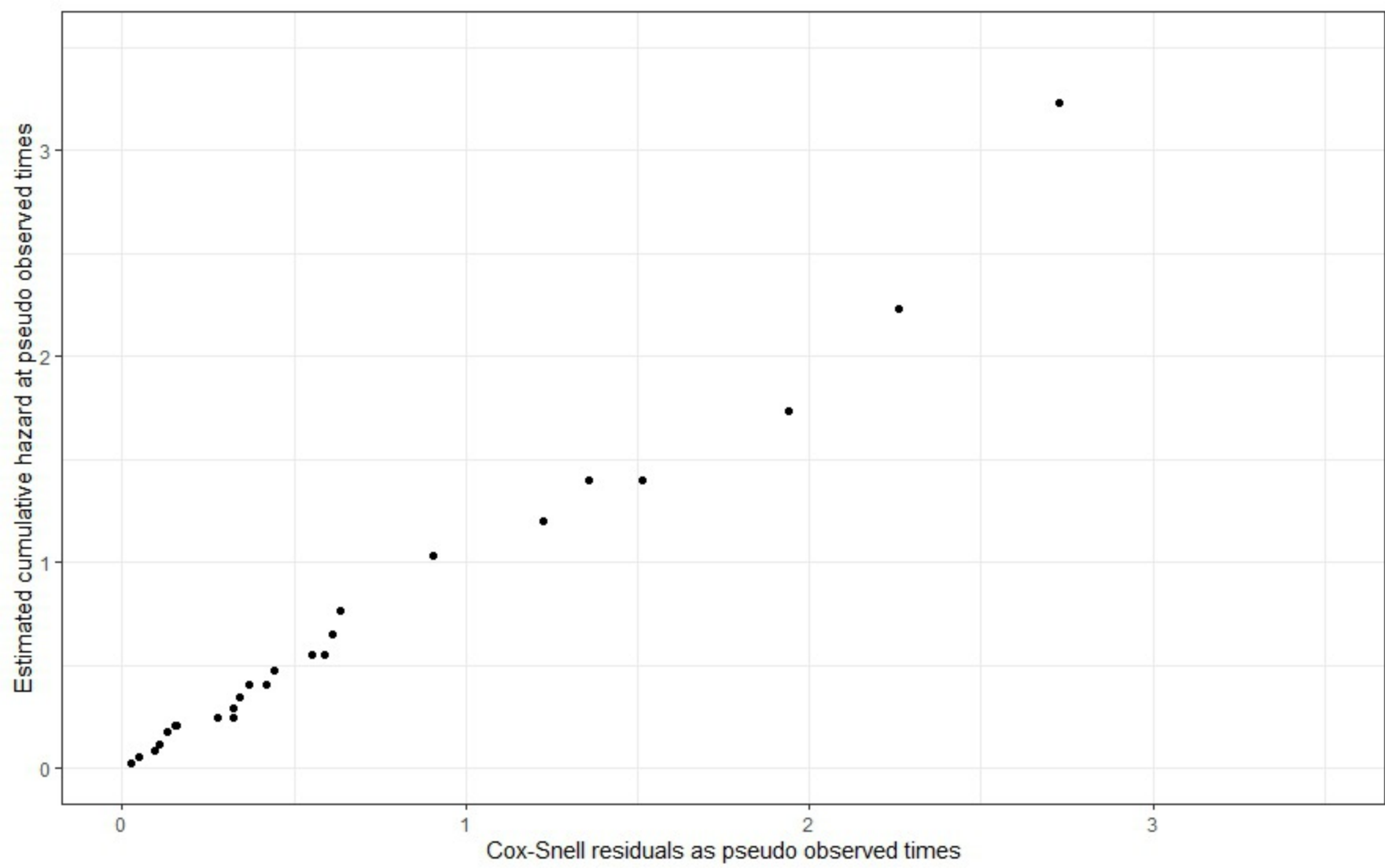
Unenhanced T1W image**T1W arterial phase image****Substracted image****Pre-TARE****Post-TARE**

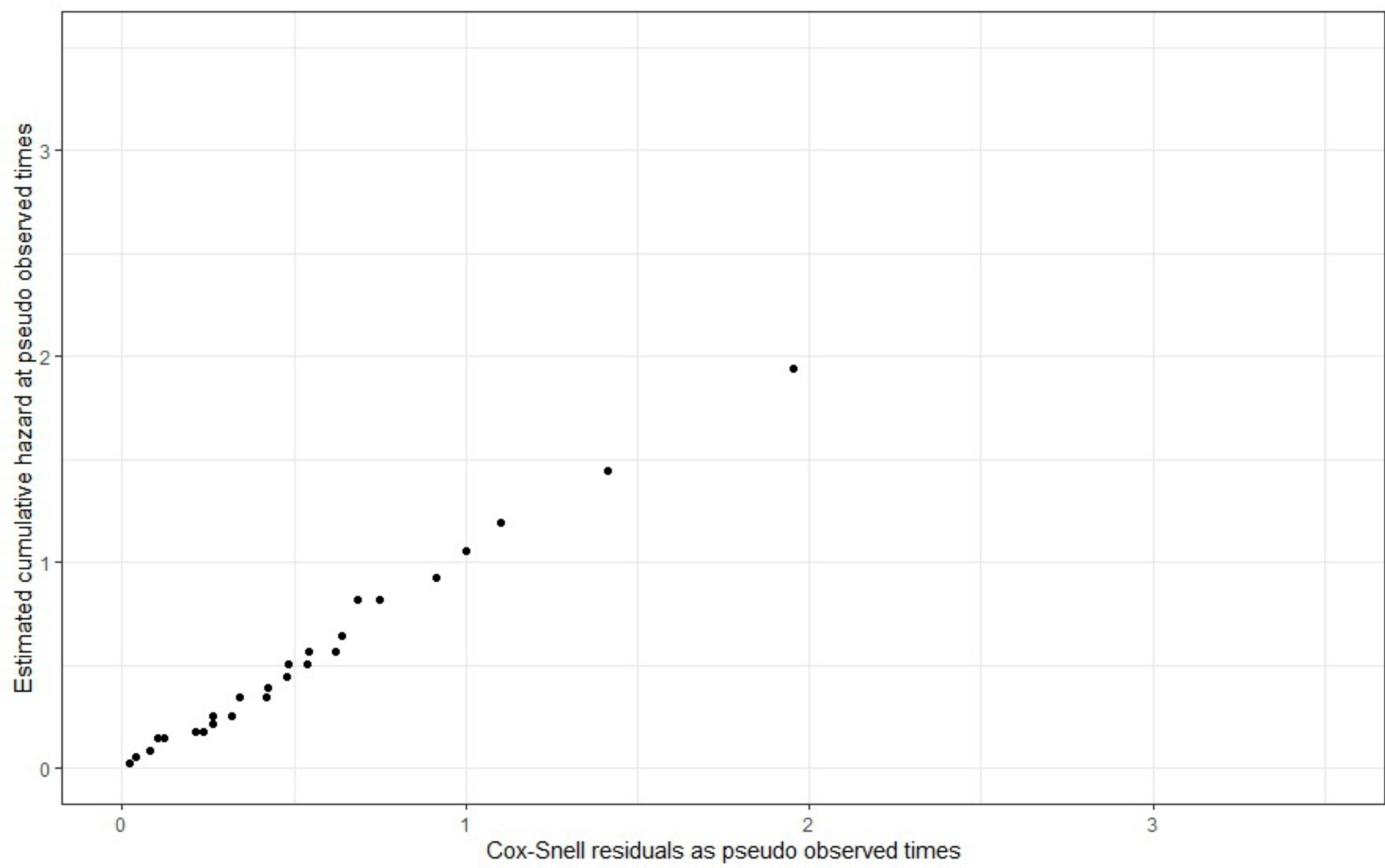


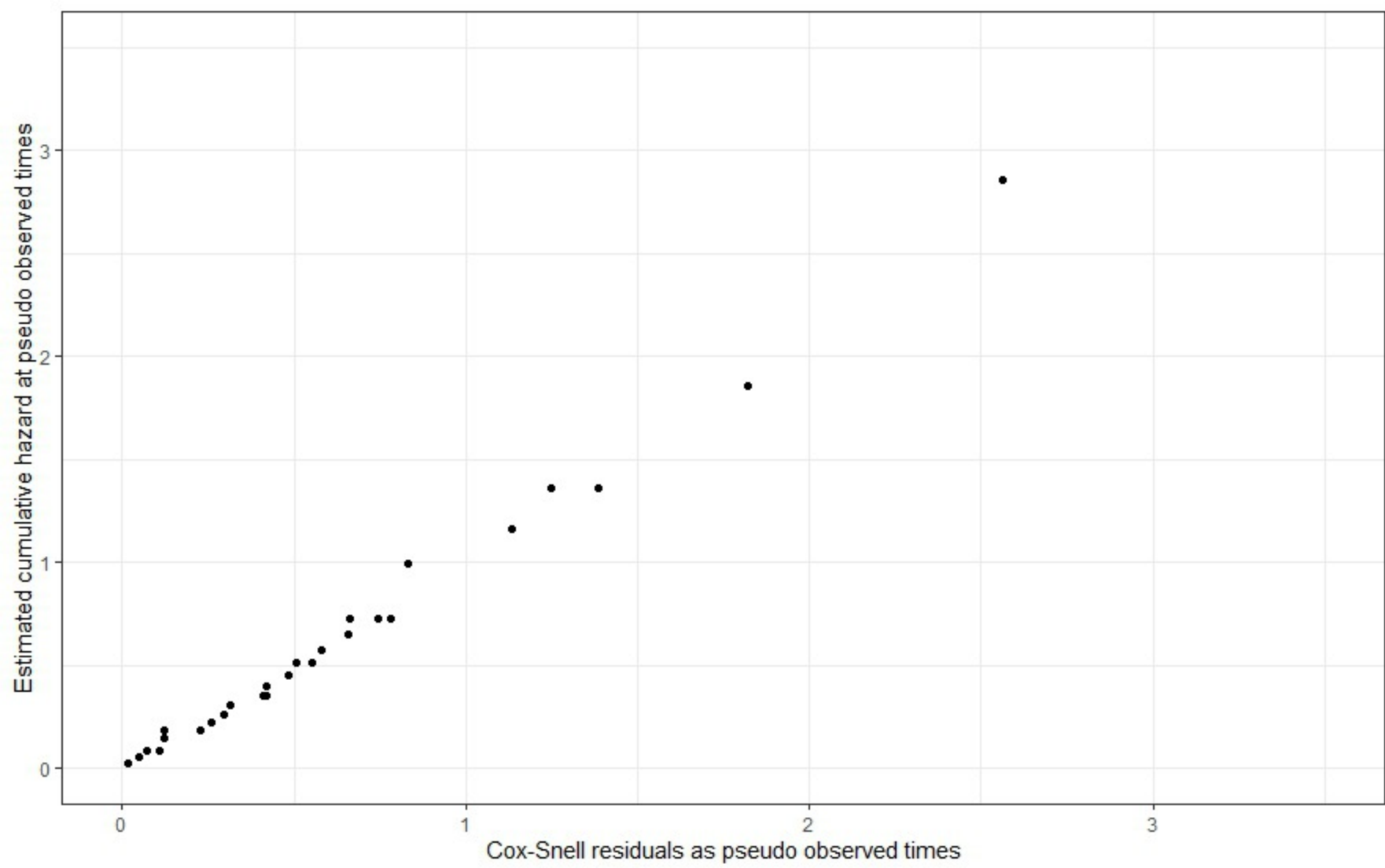












1.5-T MR scanner (Magnetom Avanto®, Siemens Healthineers)

| Sequence | T1W VIBE Dixon | Breath-hold FS TSE T2W | HASTE | Dynamic 3D VIBE ** |
|--------------------------------|-------------------|---------------------------|------------|-----------------------|
| Plane | Axial | Axial | Axial | Axial |
| Lecture/Phase FOV (mm × mm) | 380/308.94 | 400/400 | 360/292.68 | 351/282.9 |
| Slice thickness (mm) | 3 | 5 | 3 | 3 |
| Repetition time (ms) | 6.69 | 3160 | 1000 | 4.71 |
| Echo time (ms) | 2.39/4.77* | 101 | 91 | 2.15 |
| Flip angle (°) | 10 | 138 | 160 | 15 |
| Bandwidth (Hz/pixel) | 470 | 781 | 710 | 350 |
| Fat suppression | N.A. | FS | N.A. | FS |

3-T MR scanner (Magnetom Skyra®, Siemens Healthineers)

| Sequence | T1W VIBE Dixon | Breath-hold FS TSE T2W | HASTE | Dynamic 3D VIBE ** |
|--------------------------------|-------------------|---------------------------|------------|-----------------------|
| Plane | Axial | Axial | Axial | Axial |
| Lecture/Phase FOV (mm × mm) | 380/308.94 | 380/380 | 360/292.68 | 350/350 |
| Slice thickness (mm) | 3 | 5 | 3.5 | 3 |
| Repetition time (ms) | 3.97 | 2370 | 1000 | 68.77 |
| Echo time (ms) | 1.29/2.52* | 99 | 118 | 1.52 |
| Flip angle (°) | 9 | 110 | 120 | 30 |
| Bandwidth (Hz/pixel) | 1040 | 781 | 710 | 400 |
| Fat suppression | N.A. | FS | NA | FS |

FOV= Field of view; FS= fat suppressed; HASTE= half-Fourier acquisition single-shot turbo spin-echo; N.A.= not applicable; T1W= T1-weighted; T2W= T2-weighted; TSE= Turbo spin echo; VIBE= volumetric interpolated breath-hold examination.

* in phase/out phase echo times; **same acquisition parameters were used for unenhanced, hepatic arterial, portal and delayed phases

| | | |
|---|-----------------|-----------------|
| Category | | |
| Age (years) ≥ 65 | | 15 (15/37; 41%) |
| Male | | 34 (34/37; 92%) |
| Method of diagnosis | | |
| | Biopsy | 18 (18/37; 49%) |
| | Imaging | 19 (19/37; 51%) |
| Etiology of hepatopathy | | |
| | Alcohol | 7 (7/37; 19%) |
| | HCV | 6 (6/37; 16%) |
| | HCV + alcohol | 1 (1/37; 3%) |
| | HBV | 7 (7/37; 19%) |
| | NASH | 2 (2/37; 5%) |
| | NASH + alcohol | 8 (8/37; 21%) |
| | NASH + HCV | 1 (1/37; 3%) |
| | NASH + HBV | 1 (1/37; 3%) |
| | Hemochromatosis | 2 (2/37; 5%) |
| | Cryptogenic | 1 (1/37; 3%) |
| | No hepatopathy | 1 (1/37; 3%) |
| Cirrhosis | | 30 (30/37; 81%) |
| α-Fetoprotein level > 200 ng/mL | | 21 (21/37; 57%) |
| Child-Pugh class | | |
| | A | 30 (30/37; 81%) |
| | B | 7 (7/37; 19%) |
| BCLC Stage | | |
| | B | 12 (12/37; 32%) |
| | C | 25 (25/37; 68%) |
| Tumors diameter > 5 cm | | 24 (24/37; 65%) |
| Total No. of TARE interventions | | |
| | 1 | 23 (23/37; 62%) |
| | 2 | 14 (14/37; 38%) |
| Portal vein thrombosis | | 24 (24/37; 65%) |
| Ill-defined tumor borders | | 19 (19/37; 51%) |

Results are expressed as raw numbers; numbers in parentheses are proportions followed by percentages. BCLC= Barcelona Clinic Liver Cancer; HBV= Hepatitis B virus infection; HCV= Hepatitis C virus infection; NASH= Nonalcoholic steatohepatitis; TARE= transcatheter arterial yttrium-90 radioembolization.

| <i>Category</i> | <i>Included</i> | <i>Excluded</i> | <i>P value</i> |
|---|-----------------|-------------------|----------------|
| Age (years) ≥ 65 | 15 (15/37; 41%) | 12 (12/33; 36%) | 0.39 |
| Male | 34 (34/37; 92%) | 26 (26/33; 79%) | 0.13 |
| Method of diagnosis | | | 0.61 |
| Imaging | 19 (19/37; 51%) | 11 (11/33; 33%) | |
| Etiology of hepatopathy | | | 0.004 |
| Alcohol | 7 (7/37; 19%) | 3 (3/33; 9%) † | |
| HCV | 6 (6/37; 16%) | 6 (6/33; 18%) | |
| HCV + alcohol | 1 (1/37; 3%) | 1 (1/33; 3%) | |
| HBV | 7 (7/37; 19%) | 3 (3/33; 9%) | |
| NASH | 2 (2/37; 5%) | 5 (5/33; 15%) | |
| NASH + alcohol | 8 (8/37; 21%) | 3 (3/33; 9%) | |
| NASH + HCV | 1 (1/37; 3%) | 0 (0/33; 0%) | |
| NASH + HBV | 1 (1/37; 3%) | 0 (0/33; 0%) | |
| Hemochromatosis | 2 (2/37; 5%) | 0 (0/33; 0%) | |
| Cryptogenic | 1 (1/37; 3%) | 0 (0/33; 0%) | |
| No hepatopathy | 1 (1/37; 3%) | 2 (2/33; 6%) | |
| Cirrhosis | 30 (30/37; 81%) | 18 (18/33; 55%) | 0.54 |
| α-fetoprotein level > 200 ng/mL | 21 (21/37; 57%) | 11 (11/33; 33%) | 0.66 |
| Child-Pugh class | | | 0.01 |
| A | 30 (30/37; 81%) | 18 (18/33; 55%) § | |
| B | 7 (7/37; 19%) | 6 (6/33; 18%) | |
| BCLC Stage | | | |
| B | 12 (12/37; 32%) | 8 (8/33; 24%) † | 0.005 |
| C | 25 (25/37; 68%) | 17 (17/33; 52%) | |
| Tumors diameter > 5 cm | 24 (24/37; 65%) | 14 (14/33; 42%) | 0.36 |
| Total number of TARE | | | |
| 1 | 23 (23/37; 62%) | 26 (26/33; 79%) | 0.57 |
| 2 | 14 (14/37; 38%) | 7 (7/33; 21%) | |
| Portal vein thrombosis | 24 (24/37; 65%) | 15 (15/33; 45%) | 0.78 |
| Ill-defined tumor borders | 19 (19/37; 51%) | 13 (13/33; 39%) | > 0.99 |

BCLC= Barcelona Clinic Liver Cancer; HBV= Hepatitis B Virus infection; HCV= Hepatitis C Virus infection; NASH= Nonalcoholic steatohepatitis; TARE= transcatheter arterial yttrium-90 radioembolization.

Bold indicates significant *P* value

† 8 patients with missing data

‡ 10 patients with missing data

§ 9 patients with missing data

| Clinical and biological factors | Patients | Events | Univariate analysis | | |
|---------------------------------|-----------------|-----------------|---------------------|------------|-------------------|
| | | | HR | 95% CI | P |
| Age \geq 65 years | 15 (15/37; 41%) | 10 (10/20; 50%) | 1.11 | 0.48- 2.58 | 0.81 |
| AFP > 200 ng/mL | 19 (19/37; 51%) | 12 (12/20; 60%) | 1.21 | 0.51- 2.89 | 0.67 |
| Child-Pugh B | 7 (7/37; 19%) | 4 (4/20; 20%) | 0.94 | 0.32- 2.80 | 0.92 |
| BCLC C | 25 (25/37; 68%) | 15 (15/20; 75%) | 1.38 | 0.56- 3.39 | 0.48 |
| Cirrhosis | 30 (30/37; 81%) | 19 (19/20; 95%) | 1.30 | 0.38- 4.47 | 0.67 |
| Tumor size > 5 cm | 24 (24/37; 65%) | 15 (15/20; 75%) | 1.26 | 0.51- 3.10 | 0.62 |
| Portal vein thrombosis | 24 (24/37; 65%) | 14 (14/20; 70%) | 1.17 | 0.49- 2.80 | 0.72 |
| Previous curative treatments | 20 (20/37; 54%) | 12 (12/20; 60%) | 0.98 | 0.42- 2.27 | 0.96 |
| MELD > 9 | 20 (20/37; 54%) | 13 (13/20; 65%) | 1.07 | 0.42- 2.70 | 0.89 |
| Surgery after TARE | 11 (11/37; 30%) | 3 (3/20; 15%) | 0.25 | 0.07- 0.84 | 0.03 |
| Estimated dose to tumor (Gy) | - | - | 0.99 | 0.99- 1.00 | 0.86 |
| Imaging response | | | | | |
| RECIST responder | 16 (16/37; 43%) | 5 (5/20; 25%) | 0.19 | 0.07- 0.53 | 0.002 |
| mRECIST responder | 21 (21/37; 57%) | 7 (7/20; 35%) | 0.17 | 0.07- 0.42 | < 0.001 |
| EASL responder | 20 (20/37; 54%) | 6 (6/20; 30%) | 0.17 | 0.06- 0.44 | < 0.001 |
| vRECIST responder | 12 (12/37; 32%) | 4 (4/20; 20%) | 0.29 | 0.10- 0.87 | 0.03 |
| qEASL responder | 17 (17/37; 46%) | 6 (6/20; 30%) | 0.27 | 0.10- 0.69 | 0.006 |
| LI-RADS responder | 13 (13/37; 35%) | 5 (5/20; 25%) | 0.46 | 0.17- 1.24 | 0.13 |

AFP= α -fetoprotein level; BCLC= Barcelona Clinic Liver Cancer; EASL= European Association for Study of the Liver; LI-RADS= Liver Imaging Reporting and Data System; MELD= Model for End-Stage Liver Disease; No= number; mRECIST= modified Response Evaluation Criteria in Solid Tumors; qEASL= quantitative EASL; RECIST= Response Evaluation Criteria in Solid Tumors; TARE= transcatheter arterial yttrium-90 radioembolization; vRECIST= volumetric RECIST.

Bold indicates significant *P* value.

| Multivariate analysis | | | | | | |
|------------------------|-----------------|--------------------|------|------------|--------------|-------------------|
| | Patients | Median OS (months) | HR | 95% CI | P | Harrell's C-index |
| Model 1 | | | | | | |
| RECIST responders | 16 (16/37; 43%) | - | 0.26 | 0.09- 0.75 | 0.01 | 0.72 |
| RECIST non-responders | 21 (21/37; 57%) | 9.47 | 1 | - | | |
| Surgery after TARE | 11 (11/37; 30%) | - | 0.43 | 0.12- 1.56 | 0.20 | |
| No surgery after TARE | 26 (26/37; 70%) | 11.1 | 1 | - | | |
| Model 2 | | | | | | |
| mRECIST responders | 21 (21/37; 57%) | - | 0.22 | 0.08- 0.59 | 0.003 | 0.73 |
| mRECIST non-responders | 16 (16/37; 43%) | 8.05 | 1 | - | | |
| Surgery after TARE | 11 (11/37; 30%) | - | 0.49 | 0.13- 1.89 | 0.30 | |
| No surgery after TARE | 26 (26/37; 70%) | 11.1 | 1 | - | | |
| Model 3 | | | | | | |
| EASL responders | 20 (20/37; 54%) | - | 0.22 | 0.07- 0.63 | 0.005 | 0.71 |
| EASL non-responders | 17 (17/37; 46%) | 9.47 | 1 | - | | |
| Surgery after TARE | 11 (11/37; 30%) | - | 0.55 | 0.14- 2.19 | 0.40 | |
| No surgery after TARE | 26 (26/37; 70%) | 11.1 | 1 | - | | |
| Model 4 | | | | | | |
| vRECIST responders | 12 (12/37; 32%) | - | 0.38 | 0.12- 1.17 | 0.09 | 0.68 |
| vRECIST non-responders | 25 (25/37; 68%) | 10.9 | 1 | - | | |
| Surgery after TARE | 11 (11/37; 30%) | - | 0.32 | 0.09- 1.12 | 0.08 | |
| No surgery after TARE | 26 (26/37; 70%) | 11.1 | 1 | - | | |
| Model 5 | | | | | | |
| qEASL responders | 17 (17/37; 46%) | - | 0.30 | 0.12- 0.80 | 0.02 | 0.70 |
| qEASL non-responders | 20 (20/37; 54%) | 9.47 | 1 | - | | |
| Surgery after TARE | 11 (11/37; 30%) | - | 0.29 | 0.08- 1.01 | 0.05 | |
| No surgery after TARE | 26 (26/37; 70%) | 11.1 | 1 | - | | |

CI= confidence interval; EASL= European Association for Study of the Liver; HR= hazard ratio; mRECIST= modified Response Evaluation Criteria in Solid Tumors; OS= overall survival; qEASL= quantitative EASL; RECIST= Response Evaluation Criteria in Solid Tumors; TARE= transcatheter arterial yttrium-90 radioembolization; vRECIST= volumetric RECIST.

| Imaging response method | Overall response concordance (responders vs. non- responders) | | |
|-------------------------|---|-------------|----------------|
| | Fleiss Kappa | 95% CI | <i>P</i> value |
| RECIST 1.1 | 0.77 | 0.58 - 0.96 | < 0.01 |
| mRECIST | 0.57 | 0.38 - 0.75 | < 0.01 |
| EASL | 0.63 | 0.45 - 0.83 | < 0.01 |
| vRECIST | 0.46 | 0.28 - 0.65 | < 0.01 |
| qEASL | 0.42 | 0.24 - 0.61 | < 0.01 |
| LI-RADS | 0.46 | 0.29 - 0.66 | < 0.01 |

EASL= European Association for Study of the Liver; LI-RADS= Liver Imaging Reporting and Data System; mRECIST= modified Response Evaluation Criteria in Solid Tumors; qEASL= quantitative EASL; RECIST= Response Evaluation Criteria in Solid Tumors; vRECIST= volumetric RECIST.