# Centrally located small unifocal hepatocellular carcinoma between minor conservative liver resection and major hepatectomy.
## Case reports

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**Centrally located small unifocal hepatocellular carcinoma between minor conservative liver resection and major hepatectomy. Case reports.**

*Hepatocellular carcinoma (HCC) is one of the leading cancer in the world, susceptible to potentially curative liver resection (LR) in selected cases. Centrally located HCC (CL-HCC) are sited in central liver segments and may require complex LR because of their relationship to major vascular and biliary structures and deep parenchymal location. Even though extended segment-oriented resections are recommended for oncological reasons, more conservative LR may be indicated in patients with cirrhosis to preserve an adequate function of the future remnant liver (FRL). To extend the indication to LR and to increase the safety of the surgical procedure, preoperative portal vein embolization (PVE) or sequential transarterial embolization/chemoembolization (TAE/TACE) and PVE have been widely used, to induce atrophy of the embolized segments involved by the tumor and compensatory hypertrophy of the FLR. The most appropriate surgical strategy for small uninodular CL-HCC remains controversial, and should be decided according to the features of the tumor at preoperative imaging, the relationship with major intrahepatic vessels and the expected function of the FRL.*
*We report here two cases of elderly cirrhotic patients with unifocal small CL-HCC, where the surgical strategy was decided according to the kind of relationship of the tumor with the hepatic hilum at preoperative imaging. In the first case there was no clear evidence of neoplastic infiltration of the hilar vessels, so that a minor conservative LR was preferred. In the second patient the tumor was suspected to infiltrate the right portal vein, and a major LR was performed after sequential TACE/PVE.*

KEY WORDS: Centrally located, Future remnant liver, Hepatocellular carcinoma, Liver cirrhosis, Liver resection, Portal vein embolization, Transarterial chemoembolization

## Introduction

Hepatocellular carcinoma (HCC) is one of the leading cancer in the world and a common cause of death among cirrhotics [1,2]. In some western countries including Italy, hepatitis B virus (HBV) and hepatitis C virus(HCV) related HCC are progressively decreasing, whereas the incidence of tumors related to non-alcoholic fatty liver disease (NAFLD), cryptogenetic and non-viral multifactorial liver diseases is definitely increasing [3,4]. The progressive diffusion of surveillance programs in patients at risk of developing HCC may allow earlier diagnosis, when the stage of the tumor is still susceptible to potentially curative therapies including liver transplantation, surgical resection and percutaneous local ablative therapies, as in the case of small, single HCC occurring in compensated cirrhosis [5-9].

Liver resection (LR) represents one of the most valuable curative options for HCC [1,6,7,8,10]. LR should involve resection of the primary tumor with enough margin to achieve potentially curative treatment. Even though anatomic resection (AR) is widely considered the optimal surgical strategy [7,8,11-14], diseased livers have limited functional reserve and poor regeneration capacity, so that the preservation of liver tissue may be crucial in cirrhotics, as excessive resection may cause postoperative liver failure and also reduce the chance of reresection in case of recurrence [7,13]. For these reasons, non-anatomical liver resections (NAR) are reasonable alternatives in selected cases, according to the presence of the underlying cirrhosis, as well as to the size, location, and multifocality of the tumor [14].

Centrally located HCC (CL-HCC) are sited in central segments of the liver and may require extensive LR because of their relationship to major vascular and biliary structures and deep parenchymal location, with a significant risk of postoperative liver failure, especially in cirrhotics [15,16]. Even though extended segment-oriented resections are still recommended for oncological reasons [15,17], deeply located HCC close to major hepatic vessels may require in selected cases more conservative resections, with careful dissection from the vascular surface and virtually no resection margin, to preserve an adequate future remnant liver (FLR) function [16]. To extend the indication to LR and to increase the safety of the surgical procedure in HCC patients with chronic liver disease and possibly compromised postoperative liver regeneration, preoperative portal vein embolization (PVE), which induces atrophy of the embolized liver segments involved by the tumor and compensatory hypertrophy of the FLR, has been widely used [8,18,19]. A remarkable side effect of PVE is however the enhanced progression rate of the tumor [19,20]. The risk of tumor growth after PVE is probably more frequent in advanced HCC, larger than 50 mm, multifocal or with segmental portal vein thrombosis [19]. In these situations the combination of trans-arterial embolization (TAE) or trans-arterial chemo-embolization (TACE) and PVE can be indicated, because of the well documented favorable effect on atrophy of the embolized hepatic segments and on hypertrophy of the FLR, along with the prevention of tumor progression while waiting for LR[18,21].

We report here two cases of elderly patients with single small centrally-located HCC occurring in HCV-related cirrhosis, where the surgical strategy was decided according to the kind of relationship of the tumor with the vessels at the hepatic hilum. In the first patient an accurate preoperative evaluation did not show clear neoplastic infiltration of the hilar vessels, so that a minor conservative resection was preferred to preserve liver function. In the second case the tumor was suspected to infiltrate the right portal vein, and a major liver resection was performed after sequential TACE and PVE to optimize FLR function.

## Case Report

### Case n. 1

A 72-year-old white man with HCV-related cirrhosis was referred to our unit in March 2014 with a hepatic mass
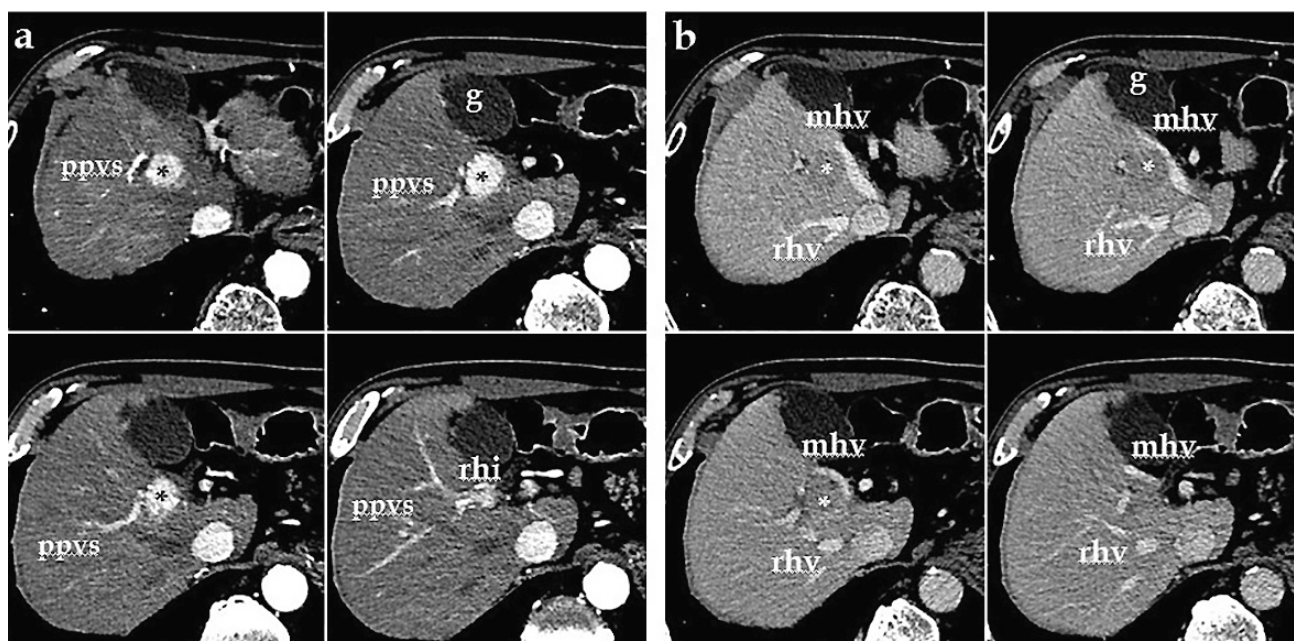


Fig. 1: A) The CT scan of the abdomen shows a 27x22 mm solid mass of segments S5-S8 (*), adjoining the right portal vein and hepatic duct and adherent to the middle hepatic vein, hyperenhancing in the late arterial phase; B) with washout in the portal venous and equilibrium phases, highly suspicious for HCC. **ppvs**: peripheral portal veins; *: neoplastic nodule ; **g**: gallbladder; **rhi**: right hepatic hilum; **rhv**: right hepatic vein; **mhv**: middle hepatic vein.
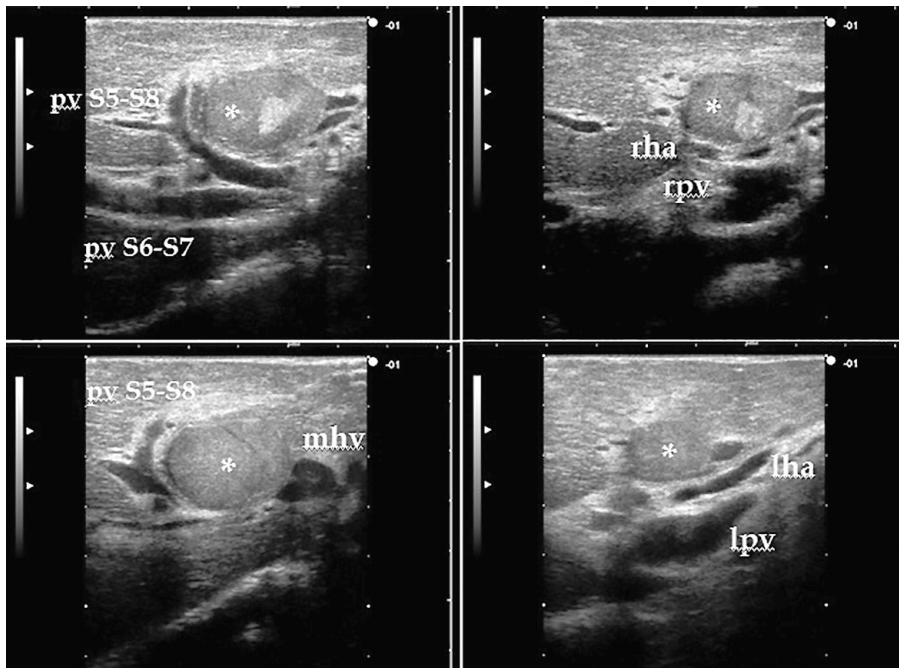
Fig. 2: The IOUS shows a dishomogeneously hypoechoic mass (*) with an hyperechoic central area and with a thin capsule, adjoining the hepatic hilum and adherent to the middle hepatic vein, but without evidence of infiltration of the vessel walls. **pv S5-S8:** right anterior portal vein for segments S5-S8; **pv S6-S7:** right posterior portal vein for segments S6-S7; *: neoplastic nodule ; **rha:** right hepatic artery; **rpv:** right portal vein; **mhv:** middle hepatic vein; **lha:** left hepatic artery; **lpv:** left portal vein.
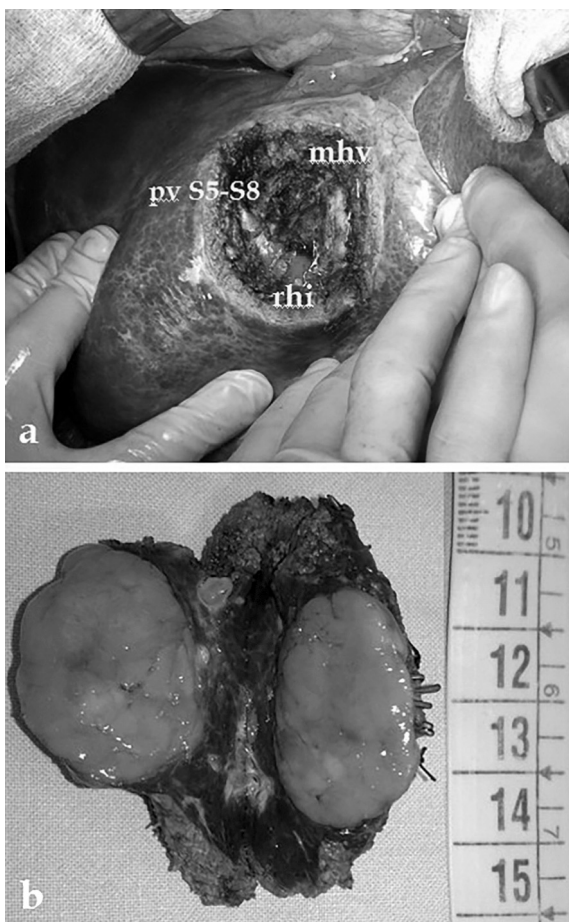


Fig. 3: A) The tumor has been cautiously detached from right anterior portal vein for segments S5-S8 (**pv S5-S8**), the right hepatic hilum (**rhi**) and the middle hepatic vein (**mhv**); A) The specimen of the conservative liver resection shows that the neoplastic nodule has been removed without evident margins.

occasionally identified on performing abdominal ultrasound as a routine evaluation for his chronic liver disease. HCV infection had been apparently eradicated with Interferon and Ribavirine treatment. His medical history additionally included ischaemic heart disease, with a miocardial infarction successfully treated with percutaneous transluminal coronary angioplasty ten years before. The laboratory data on admission revealed normal AST, ALT and bilirubin levels, normal renal function tests, low platelet count (128 x10^3/microL, reference range 150-380 x10^3/microL) and normal serum α-fetoprotein levels (2.8 ng/mL, reference range <7 ng/mL). A liver mass protocol computed tomography (CT) scan of the abdomen showed a 27x22 mm solid mass of segments S5-S8, adjoining the right portal vein and hepatic duct and adherent to the middle hepatic vein, hyperdense in the late arterial phase with washout in the portal venous and delayed phases, highly suspicious for HCC (Fig. 1); the spleen was normal; the splenic and the portal veins enhanced normally; there was no evidence of ascites and of nodal or distant metastases. A chest CT scan excluded pulmonary metastases. An esophagogastroduodenoscopy revealed low-risk esophageal varices. The Child-Pugh score was A5 and the MELD score was 7. An echocardiogram and a spirometric examination showed substantially normal cardiovascular and respiratory functions.

The accurate evaluation of the CT scan of the liver revealed a possible cleavage between the tumor and the vessels, and in the delayed phase a thin capsule was evident; on this basis we planned a wedge resection with careful dissection of the tumor from the vascular surface. Intraoperative ultrasonography (IOUS) showed a dishomogeneously hypoechoic mass with an hyperechoic central area, with a thin capsule, adjoining the hepatic hilum and adherent to the middle hepatic vein, but without evidence of infiltration
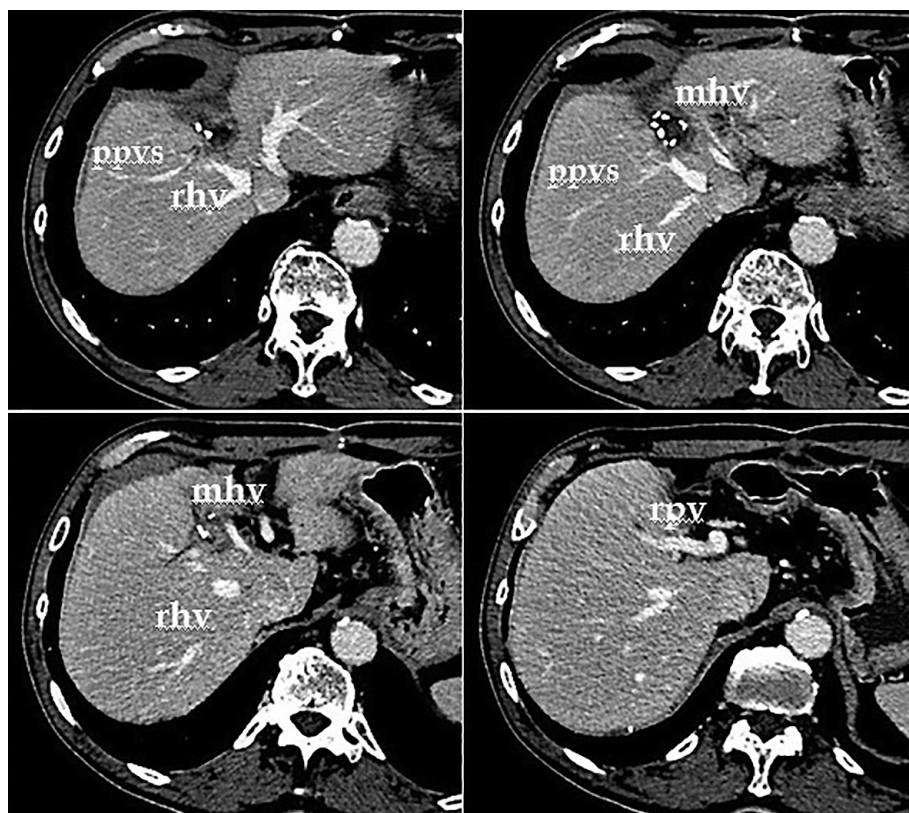
Fig. 4: The postoperative CT scan of the abdomen shows a round hypodense area without contrast enhancement surrounded by surgical clips, corresponding to the surgical scar; all the main intrahepatic vessels previously adherent to the tumor are still viable. **ppvs:** peripheral portal veins; **rhv:** right hepatic vein; **mhv:** middle hepatic vein; **rpv:** right portal vein.

of the vessel walls (Fig. 2). The portal vein was isolated at the hepatic hilum and taped for safety. IOUS-guided hepatic transection was performed with the usual technique[22], with 10 minutes of hepatic pedicle clamping; the tumor was gently detached from the right and the left portal veins and the middle hepatic vein, respectively, along its capsule (Fig. 3). At the end of liver resection, the intraoperative echodoppler examination demonstrated a normal blood flow in the right and left portal veins and in the middle hepatic vein, respectively, with adequate perfusion of the remnant liver parenchyma. The hepatic stump was carefully inspected for bleeding and bile leak (Fig. 3a). Grossly examination showed a lobulated tumor 30 mm in diameter, with capsule formation and without macroscopic vascular infiltration (Fig. 3b); microscopic examination revealed a grade II carcinoma according to the Edmondson and Steiner system, with expansive growth pattern and without microscopic vascular infiltration; resection margins were negative.

The patient spent the first p.o. day in the intensive care unit; the postoperative course was substantially uneventful and the patient was discharged 7 days after surgery. Postoperative evaluation included ambulatory visit, routine blood and urine tests including serum α-fetoprotein levels, and contrast-enhanced thoraco-abdominal CT scan at four-month intervals for 2 years, and at six-month intervals for further three years. The patient is in good conditions without recurrence 44 months after surgery (Fig. 4).

CASE N. 2

A 70-year-old white woman with HCV-related cirrhosis was referred to our unit in June 2011 with a hepatic mass identified on performing abdominal ultrasound. The patient, who was routinely evaluated for HCV-related chronic hepatitis, was asymptomatic. Her medical history additionally included arterial hypertension with hypertensive heart disease and a previous episode of cerebral ischemic stroke without sequelae. The laboratory data on admission revealed slightly elevated AST (71 U/L, reference range <32 U/L) and ALT (96 U/L, reference range <31 U/L) levels with normal bilirubin levels, normal renal function tests, low platelet count (62 x10^3/microL, reference range 150-380 x10^3/microL) and normal serum α-fetoprotein levels (3 ng/mL, reference range <7 ng/mL). A liver mass protocol computed tomography (CT) scan of the abdomen showed a 26x23 mm solid mass of segments S5-S8, adherent to the right portal vein and hepatic duct, hyperdense in the late arterial phase with washout in the portal venous and delayed phases, highly suspicious for HCC (Fig. 5a); the spleen was normal; the splenic and the portal veins enhanced normally; there was no evidence of ascites and of nodal or distant metastases. A chest X-ray excluded pulmonary metastases. An esophagogastroduodenoscopy revealed low-risk esophageal varices. The Child-Pugh score was A5 and the MELD score was 9.

On the basis of the site of the tumor, which was centrally located and strictly adherent to the main vessels of the right
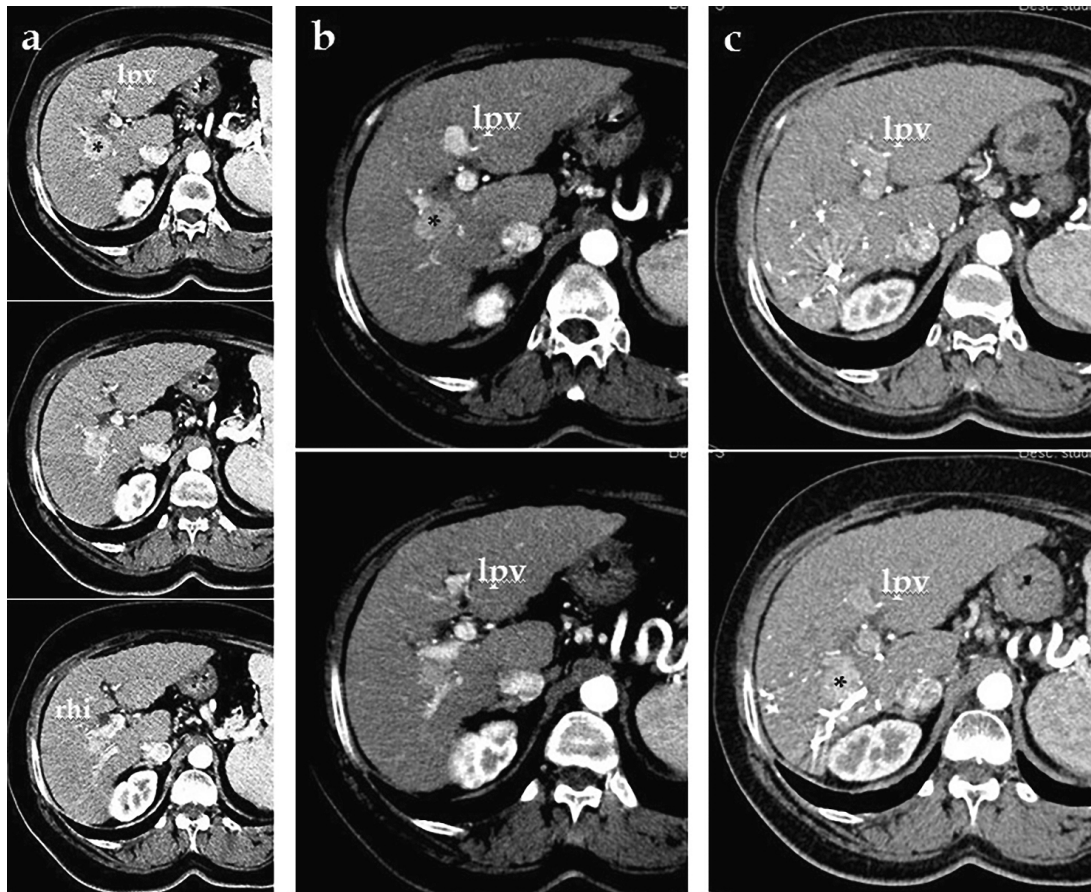
Fig. 5: A) The preoperative CT scan of the abdomen shows a 26x23 mm solid mass of segments S5-S8 (*), adherent to the right portal vein and hepatic duct, hyperdense in the late arterial phase with washout in the portal venous and delayed phases, highly suspicious for HCC; B) The CT scan of the abdomen performed one month after selective TACE of segments S5-S8 shows a 25 mm tumor still partially viable, with hyperdense areas in the late arterial phase. c) The CT scan of the abdomen performed 3 months after PVE shows that the tumor is still partially viable with hyperdense areas in the late arterial phase, but without evidence of progression; the left hemiliver has adequately hypertrophied. **lpv:** left portal vein; *: neoplastic nodule; **rhi:** right hepatic hilum.

hemiliver, and of the liver disease with substantially normal liver function, she was proposed a combination of TACE and PVE followed by right hepatectomy. In July 2011 she underwent selective arterial embolization of segments S5-S8 with epirubicin-lipiodol emulsion followed by gelatin sponge, without postoperative complications, and was discharged on 5th p.o. day. One month later, a CT scan of the abdomen showed a 25 mm solid mass still partially viable with hyperdense areas in the late arterial phase with rapid washout in the portal venous and delayed phases (Fig. 5b). The patient refused the planned PVE and the subsequent liver resection so that in November 2011 she received a second selective arterial embolization of segments S5-S8 with epirubicin-lipiodol emulsion without postoperative complications, and was discharged on 3rd p.o. day. A CT scan of the abdomen one month later showed a 25 mm solid mass with areas of viable tumor tissue. Since her clinical status was unchanged and the tumor still viable, the patient accepted the originally planned surgical strategy and in February 2012 underwent transhepatic right PVE using n-butyl cyanoacrylate and Lipiodol; preoperative

laboratory data revealed slightly elevated AST (72 U/L, reference range <32 U/L) and ALT (83 U/L, reference range <31 U/L) levels with normal bilirubin levels, normal renal function tests, low platelet count (71 x10^3/microL, reference range 150-380 x10^3/microL) and normal serum α-fetoprotein levels (4.5 ng/mL, reference range <7 ng/mL); the Child-Pugh score was A5 and the MELD score was 9; the procedure was uneventful and the patient was discharged on 4th p.o. day. The CT scan performed in May 2012 revealed a future remnant liver (FRL) volume of 578 cm(3), while the HCC features were substantially unaltered (Fig. 5c).

An echocardiogram and a spirometric examination showed substantially normal cardiovascular and respiratory functions. The planned right hepatectomy was ultimately considered feasible with a reasonable risk. Intraoperative exploration with IOUS showed a dishomogeneously iso-hyperechoic mass with hypoechoic areas, tightly adherent to the vessels for segments S5-S8 and S6-S7 without clear evidence of capsule; the right hepatic vein was isolated and taped for safety. IOUS-guided hepatic resection was performed using intermittent hepatic pedicle clamping
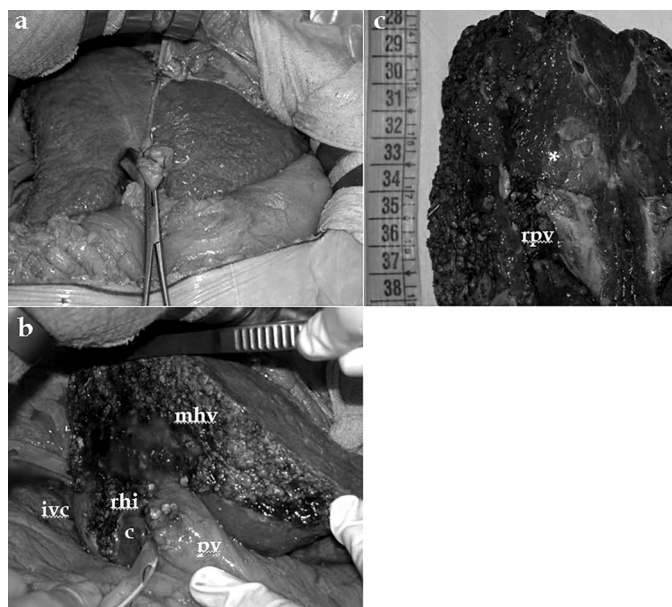
Fig. 6: A) The remnant liver corresponding to the hypertrophied left hemiliver at the end of the right hepatectomy; B) The hepatic stump, where can be recognized the portal vein (**pv**), the sutured vessels of the right hepatic hilum (**rhi**), the middle hepatic vein (**mhv**), the inferior vena cava (**ivc**) and the residual caudate lobe (c); C) The specimen of the right hepatectomy, where the HCC (*) macroscopically infiltrates the right portal vein (**rpv**).
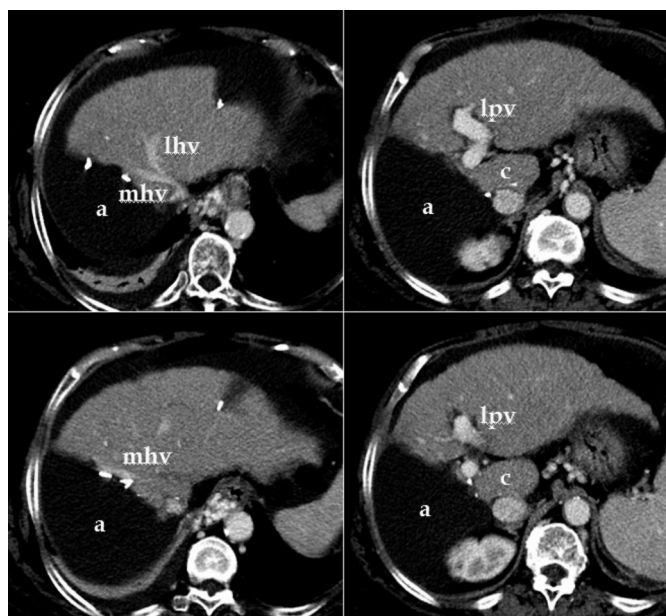


Fig. 7: The postoperative CT scan of the abdomen shows that the remnant left hemiliver has further hypertrophied; an ascitic fluid collection is also evident (**a**). **lhv:** left hepatic vein; **mhv:** middle hepatic vein; **lpv:** left portal vein; **c:** residual hypertrophied caudate lobe.

consisting of 10 minutes of ischemia followed by at least 10 minutes of reperfusion[22]; the total duration of clamping was 30 minutes. The dissection plane was accurately monitored with ultrasonography. At the end of liver resection, the intraoperative echodoppler examination demonstrated a normal blood flow in the left portal vein and in the left and middle hepatic veins, with adequate perfusion of the remnant liver parenchyma. The hepatic stump was carefully inspected for bleeding and bile leak (Fig. 6 a, b). Grossly examination showed a lobulated tumor 25 mm in diameter, without capsule formation, and with macroscopic vascular infiltration (Fig. 6c); microscopic examination revealed a grade III carcinoma according to the Edmondson and Steiner system, with areas of necrosis, and mixed expansive and infiltrative growth pattern with microscopic vascular infiltration; resection margins were negative (R0 resection).

The postoperative course was substantially uneventful and the patient was discharged 11 days after surgery; the subsequent postoperative course was complicated by mild ascites treated with diuretics (Fig. 7). Postoperative evaluation included ambulatory visit, routine blood and urine tests including serum α-fetoprotein levels, and contrast-enhanced thoraco-abdominal CT scan at four-month intervals. There was no evidence of tumor recurrence up to 20 months after surgery, when the patient developed drug-resistant acute leukemia. She died two months later of multiorgan failure.

## Discussion

Hepatocellular carcinoma is one of the leading cancer in the world and the most common cause of death among cirrhotic patients [1,2]. Mediterranean countries have intermediate incidence rates of 10-20 per 100,000 individuals [23]. In Italy, HBV and HCV related HCC significantly decreased in recent years, even though in Southern Italy the prevalence of HCV infection is still exceedingly high [3], whereas the incidence of tumors related to NAFLD, cryptogenetic and non-viral multifactorial liver diseases is noticeably increasing [4]. A progressive ageing of HCC patients has been reported in recent years in Japan and in some Western countries [5], with similar trends also in Italy, where the peak incidence has been described in septuagenarians [4]. Cirrhosis is the main risk factor for the development of HCC and about 30%-35% of all cirrhotic patients will develop HCC over time [5].

The progressive diffusion of surveillance programs in patients at risk of developing HCC may allow earlier diagnosis, when the stage of the tumor is still susceptible to potentially curative therapies with expected 5-year survival rates beyond 50-70%, such as liver transplantation, surgical resection, either open or laparoscopic, and percutaneous local ablative therapies, including radiofrequency ablation (RFA), ethanol injection and microwave coagulation therapy [5-8], as in the case of small, unifocal HCC in patients with compensated cirrhosis. LR represents one of the most

valuable curative options for HCC, even though its place in the management of HCC patients is still debated [1,7,8]. A recent overview of meta-analyses comparing the results of the management of HCC has shown that LR is superior to RFA for the improvement of overall survival rates [10]. Similar conclusions have been drawn for small HCC, with LR being superior to nonsurgical ablative therapies and with RFA being the most effective single nonsurgical ablative treatment [6].

LR should involve resection of the primary tumor with enough margin to prevent recurrence and to achieve potentially curative treatment. Since HCC has high propensity for vascular invasion and metastatic spread through the portal venous system, AR is widely considered the optimal surgical strategy because eradicates portal tributaries close to the tumor, possibly reduces the risk of local tumor spread and may ultimately determine a survival benefit, as demonstrated by a number of studies comparing AR versus NAR for HCC [7,8,11,13,14]. However AR sacrifices more non-tumorous liver parenchyma than NAR; since cirrhotic livers have limited functional reserve and poor regeneration capacity, the preservation of liver tissue is critical, as excessive resection may cause postoperative liver failure, and may also reduce the chance of reresection in case of multicentric recurrence, so adversely affecting the long-term survival after LR[7,13]. The difference observed between anatomical and non-anatomical resections in terms of long-term results substantially disappears for smaller HCC, probably because smaller tumors are frequently encapsulated and have lower incidence of venous invasion[2,24]. In a study based on the nationwide Japanese database of the LCSGJ including 72,744 patients with single HCC who received curative LR, the overall survival seemed to be better after AR than NAR, but without definite statistical significance (P = 0.0531), while the disease-free survival was significantly better after AR (P = 0.0089); when stratified by tumor size (<2, 2-5, and >5 cm), disease-free survival was increased after AR of tumors 2-5 cm in size (P = 0.0005), but was similar between the two treatment groups for HCCs <2 cm and >5 cm, respectively; further stratification according to liver damage did not show any significant difference between the two treatment groups; the authors concluded that AR are recommended, but NAR should be considered an alternative treatment option for single HCC, if an anatomical resection cannot be performed safely [25].

Also the optimal resection margin at LR remains controversial[12]. Ikai et al evaluated the prognostic predictors of survival in a series of 12,118 patients with HCC in a Japanese nationwide database who underwent LR between 1990 and 1999; surgical curability and free surgical margins were independent prognostic predictors at multivariate analysis, along with age, degree of liver damage, alpha-fetoprotein level, maximal tumor dimension, number of tumors, intrahepatic extent of tumor, extrahepatic metastasis, portal vein invasion and hepatic vein invasion[26]. However a recent meta-analysis evaluating the influence of the width of resection margin for HCC on recurrence and

survival rates could not find any significant difference between patients with resection margin <1 cm and those with resection margin ≥1 cm in recurrence rates (P=0.08), and in 1-year (P=0.75), 3-year (P=0.53) and 5-year (P=0.15) survival rates, respectively [27]. As for the type of LR, also the impact of the margin status might be related to tumor characteristics, including size and stage. Even though the precise role of the type, extent and margin status of the LR are still debated, a surgical strategy that prefers AR with adequate free margins should be adopted whenever possible in order to achieve optimal oncologic results, minimize the risk of local recurrence and obtain satisfactory overall and disease free survivals [11]. Nonetheless, non-anatomical and/or marginal LR are reasonable alternatives when appropriate, according to the presence and functional reserve of the underlying cirrhosis, as well as to the size, location, and multifocality of the tumor.

CL-HCC are sited in Couinaud segments S4, S5 or S8 of the liver and may require extensive LR because of their relationship to major vascular and biliary structures and deep parenchymal location [15]. A revised definition describes CL-HCC as 'carcinoma adjoined to the porta hepatis, less than 1 cm from major vascular structures, including the inferior vena cava (IVC), the main portal branches as well as the main trunks of the hepatic veins, and usually located in Couinaud segment' S1, S4, S5, S8, or at the junction of the central segments' [15,16]. These tumors represent a real challenge, especially in cirrhotic patients, where extensive LR with adequate surgical margins are usually not possible due to insufficient FLR and/or underlying hepatic dysfunction. Usually, these centrally located tumors are excised with major resections such as conventional or extended right or left hemihepatectomy or even central hepatectomy or mesohepatectomy [15], especially when HCC are larger than 3 cm [17]. Extended segment-oriented resections are recommended for oncological reasons, but carry the risk of significant blood loss, longer operative time and also postoperative liver failure, especially in patients with cirrhosis or compromised hepatic functional reserve. Even though some authors claim for adequate resection margins of at least 20 mm also for centrally located tumors [7], in most cases of deeply located HCC very close or somehow adherent to major hepatic vessels adequate resection margins are difficult to achieve, and the only option to perform potentially curative tumor removal and preservation of adequate FLR function may be careful dissection from the vascular surface without a real margin [16].

The impact of the width of the resection margin for CL-HCC is still debated [12,17]. Yu et al have recently reported a series of 118 patients who underwent a R1 LR with exposure of tumor surface for CL-HCC adherent to portal veins (29.7%), hepatic veins (59.3%), or both (11.0%) [16]; HCC were resectable but adherent to or compressing major vascular structures; patients had an adequate performance status but were unable to tolerate major hepatectomy; all tumors were >3cm, with a median diameter of 4.5 cm, and were uninodular in 88.1% of cases; the results were

compared with those of 169 patients who underwent conventional hepatectomy without exposure of the tumor. The 1-, 3-, and 5-year overall survival rates were 92.3, 70.3, and 44.9%, respectively, in the exposure group and 97.8, 81.4, and 53.1%, respectively, in the control group; the difference was not significant (P = 0.094). However the 1-, 3-, and 5-year recurrence-free survival rates were significantly worse in the exposure group, 74.4, 45.6, and 30.1%, respectively, than in the control group, 80.9, 57.2, and 31.7%, respectively (P = 0.041). The multivariate analysis of prognostic factors for patients resected with exposure of tumor surface identified tumor diameter, tumor differentiation and the presence of satellite nodules as independent prognostic predictors of survival, and tumor diameter, tumor differentiation, the presence of satellite nodules and chronic hepatitis as independent prognostic predictors of recurrence. In a previous series of 62 patients who underwent LR with exposure of the tumor surface and were compared with 365 patients resected without exposure of the tumor surface, Matsui et al did not observe significant differences regarding overall survival, overall recurrence rates, recurrence rates at the cut stump or the number and the location of intrahepatic recurrences[28]. It should be noted however that this series included tumors at an earlier stage than that reported by Yu et al, since HCC with tumor exposure were <3 cm in 37.1% of the cases and were capsulated in 86.9%. In another series of 196 patients who received central hepatectomy for centrally located large (>3 cm) HCC involving either 2 or 3 segments (Couinaud segments S4, S5, S8), Jeng et al compared outcomes between 172 patients with >5 to <10 mm and 24 with <5 mm as their narrowest margin width [17]. Even though patients with narrowest margin width <5 mm had more advanced tumors and the marginal intrahepatic recurrence (i.e. within 20 mm from resection margin) was significantly more frequent, the cumulative overall and disease-free survivals were similar to those with narrowest margin width >5 to <10 mm.

In our first patient the preoperative CT scan showed a HCC <3 cm of segments S5-S8, with a thin capsule in the delayed phase, adjoining the right portal vein and hepatic duct and adherent to the middle hepatic vein, but with a possible cleavage between the tumor and the vessels; on this basis we planned a conservative wedge resection with careful dissection of the tumor from the vascular surface to prevent postoperative liver dysfunction; the IOUS confirmed the absence of infiltration of the vessel walls and the planned resection was performed; the postoperative course was uneventful without signs of liver failure and the patient is alive without recurrence 44 months after surgery.

Since CL-HCC mainly develops in patients with chronic liver disease, where major LR may frequently result in inadequate postoperative regeneration and subsequent liver failure, preoperative PVE has been widely used to extend the indication to LR and to increase the safety of the procedure [8,19]. Preoperative PVE induces atrophy of the embolized liver segments involved by the tumor and compensatory hypertrophy of the FLR, and its usefulness has been demonstrated either for primary or for metastatic liver tumors [8,18,19]. However, the beneficial effect of preoperative PVE may be impaired in patients with chronic liver disease, especially liver cirrhosis, where the volumetric analysis of the FLR should be associated to an accurate evaluation of the hepatic functional reserve [18,19]. In addition to the volumetric increase of the FLR, the kinetic growth rate after PVE (i.e. the speed of increase in the volume of the FLR) has been recently demonstrated to be a better predictor of postoperative morbidity and mortality after major LR than conventional volumetric assessments [29]. As a matter of fact, preoperative PVE can be considered a valuable preoperative stress test in HCC patients with chronic liver disease where a major LR is planned [7].

A remarkable side effect of PVE is the enhanced progression rate of the tumor, which may be promoted either by the increment of arterial blood supply to the nonembolized liver segments or by the increased levels of growth factors and cytokines involved in atrophy-hypertrophy mechanisms [18]. Even though tumor progression after PVE, either intrahepatic or at extrahepatic sites, may sometimes preclude the planned surgical strategy, PVE per se does not seem to have an adverse effect on long-term prognosis after LR [19]. Tanaka et al reported that preoperative PVE improved the survival rate after right hepatectomy in HCC patients with impaired liver function; moreover, the survival rate after tumor recurrence was better in patients with sufficient residual hepatic function to tolerate further treatment, including second hepatic resection, and most of the patients who underwent preoperative PVE were able to tolerate treatment for recurrent tumor, despite worse hepatic function before the original operation; the authors concluded that preoperative PVE in candidates to right hepatectomy with diseased liver may preserve hepatic function and allow treatment of tumor recurrence [20].

However in advanced tumors, larger than 50 mm, multifocal or with segmental portal vein thrombosis, the occurrence of tumor growth after PVE is probably more frequent [19]. In these situations the combination of TAE or TACE and PVE could be indicated. Sequential TAE and PVE before hepatic resection has been first reported by Kinoshita et al in 1986: in a small group of 17 patients PVE strengthened the anticancer effect of TAE, prevented intrahepatic metastases, and caused permanent hypertrophy of the FLR useful to prepare the liver parenchyma for surgery[21]. The favourable effect of TAE/TACE followed by PVE on the atrophy of the embolized hepatic segments and on the hypertrophy of the FLR in HCC patients also with diseased liver, along with the prevention of tumor progression while waiting for LR, has been subsequently confirmed by others [18]. The results of PVE and combined TACE-PVE before LR have been recently reviewed [19]: the median 90-days postoperative morbidity was 24%, 29% and 33% after preoperative PVE, combined TACE-PVE and in the control group, respectively; the median 90-days postoperative mortality was 3%, 7% and 2% after preoperative PVE, combined TACE-

PVE and in the control group, respectively; the median 5-year overall survival was 42%, 70% and 42% after preoperative PVE, combined TACE-PVE and in the control group, respectively; the median 5-year disease-free survival was 38% and 49% after preoperative PVE and combined TACE-PVE, respectively; the weighted mean 5-year disease-free survival was 20% in the control group.

In our second patient the preoperative CT scan showed a HCC <3 cm tightly adherent to the right portal vein and hepatic duct, without a clear capsule and without an evident cleavage between the tumor and the vessels. On this basis we planned sequential TACE and PVE followed by right hepatectomy, to maximize the hypertrophy of the FLR and to prevent tumor progression and infiltration of vessels at hepatic hilum. TACE was limited to segments S5-S8 to improve the tolerability of the procedure in anticipation of the subsequent PVE. Since the patient initially refused the planned PVE and the tumor vas partially viable without evidence of progression, she received a second TACE of segments S5-S8 four months later, followed by PVE and right hepatectomy, as previously planned. IOUS showed a dishomogeneous mass tightly adherent to the vessels for segments S5-S8 and S6-S7 without evidence of capsule. Gross examination of the surgical specimen showed a HCC 25 mm in diameter without capsule formation and macroscopic infiltration of the portal veins.

## Conclusion

The most appropriate surgical strategy for small uninodular CL-HCC remains controversial, and should be decided according to the features of the tumor at the preoperative imaging, to the relationship of the tumor with major intrahepatic vessels and to the expected postoperative function of the FLR. More conservative resections also without a clear resection margin can be considered for cirrhotic patients with encapsulated tumors without satellite nodules and without clear evidence of vessel infiltration, while more extensive, anatomic resections are appropriate for tumors with satellite nodules or if an infiltration of the major intrahepatic vessels is suspected. In these cases an accurate preoperative evaluation of the FLR function is mandatory, and the indication to preoperative PVE or sequential TACE and PVE should be appropriately considered.

## Acknowledgments

## Riassunto

Il carcinoma epatocellulare (HCC) è una delle neoplasie più frequenti al mondo ed una delle principali cause di decesso nei pazienti con cirrosi epatica. La progressiva diffusione di programmi di sorveglianza consente attualmente di giungere alla diagnosi precoce di neoplasie unifocali di piccole dimensioni ("small") nel contesto di un'epatopatia ben compensata, suscettibili di una resezione epatica potenzialmente curativa in casi selezionati. L'HCC centro-epatico (CL-HCC) è situato nei segmenti centrali del fegato, e può richiedere una resezione epatica complessa a causa dei rapporti con le principali strutture vascolari e biliari intraepatiche e della posizione profonda nel contesto del parenchima, con un rischio peraltro significativo di insufficienza epatica postoperatoria. Sebbene anche per queste neoplasie siano indicati interventi resettivi anatomici per motivi oncologici, in pazienti selezionati con malattia epatica cronica possono essere indicati interventi più conservativi, allo scopo di preservare un'adeguata funzione postoperatoria del fegato residuo. Per estendere l'indicazione alla resezione epatica e per aumentare la sicurezza della procedura chirurgica nei pazienti con epatopatia cronica ed eventualmente con una compromissione dell'attitudine alla rigenerazione epatica postoperatoria, sono state utilizzate particolari tecniche che precedono l'intervento resettivo, come l'embolizzazione portale (PVE) o in alternativa l'embolizzazione selettiva epatica (TAE) eventualmente associata a chemioterapia selettiva epatica (TACE), seguita dalla PVE, allo scopo di indurre l'atrofia dei segmenti epatici embolizzati sede del tumore e l'ipertrofia compensativa del fegato stimato residuo. La strategia chirurgica più appropriata per i CL-HCC unifocali "small" rimane controversa e va definita in base alle caratteristiche del tumore all'imaging preoperatorio, ai suoi rapporti con i principali vasi intraepatici ed alla funzionalità del fegato residuo dopo l'intervento. Una resezione epatica conservativa anche senza un chiaro margine di resezione può essere presa in considerazione per i pazienti cirrotici con tumori capsulati, in assenza di noduli satelliti e di una chiara infiltrazione dei vasi intraepatici, mentre le resezioni anatomiche più estese possono essere indicate per i tumori con noduli satelliti o nel sospetto di un'infiltrazione della parete vascolare. In questi casi è necessaria un'accurata valutazione preoperatoria del volume e della funzione del fegato stimato residuo, allo scopo di definire l'indicazione ad una eventuale PVE o ad una TACE seguita da PVE in preparazione alla resezione chirurgica, per limitare il rischio di un'insufficienza epatica postoperatoria.

Vengono riportati due casi di pazienti anziani con CL-HCC unifocale "small" insorti su una cirrosi epatica HCV-relata, dove la strategia chirurgica è stata decisa in base alla sede della neoplasia ed ai rapporti con le strutture vascolari intraepatiche. Nel primo caso la valutazione preoperatoria non mostrava una chiara infiltrazione neoplastica dei vasi ilari destinati all'emifegato destro e della vena sovraepatica media, ed è stata pertanto preferita una resezione atipica conservativa allo scopo di preservare la funzione epatica postoperatoria. Nel secondo caso vi era il sospetto che la neoplasia infiltrasse il ramo portale destro; si è pertanto deciso di effettuare una TACE seguita da una PVE in

preparazione all'epatectomia destra, portata successivamente a termine senza una significativa compromissione della funzione epatica postoperatoria.

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