

Percutaneous treatment versus hepatic resection for the treatment of small hepatocellular carcinoma

Le traitement percutané versus la résection chirurgicale dans la prise en charge du petit carcinome hépatocellulaire

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RÉSUMÉ

Prérequis: Le carcinome hépatocellulaire occupe la première place des tumeurs hépatiques. Le choix entre le traitement chirurgical ou le traitement percutané fait débat chez les patients ayant un carcinome hépatocellulaire à un stade précoce.

Le but de notre étude était de comparer les résultats à long terme et la survie entre traitement chirurgical et percutané des petits carcinomes hépatocellulaires.

Méthodes: Etude comparative rétrospective menée entre 2009 et 2012. L'étude a inclus tous les patients présentant un petit carcinome hépatocellulaire (classé selon les critères de Milan), répartis en deux groupes: groupe 1, incluant les patients ayant bénéficié d'un traitement chirurgical et groupe 2, les patients ayant bénéficié d'un traitement percutané. Les courbes de survie étaient réalisées par la méthode de Kaplan-Meier et comparées en utilisant le test log-rank.

Résultats: Parmi les soixante trois patients ayant un carcinome hépatocellulaire, vingt-huit avaient un petit carcinome hépatocellulaire. L'âge moyen des patients était de 63 ans. L'étiologie de la cirrhose était post virale B ou C dans la quasi-majorité des cas (96%). Le score de Child-Pugh était respectivement A et B chez 22 patients (78,5%) et 6 (21,5%) patients. Le traitement chirurgical était réalisé dans 15 cas (53,5%), le traitement percutané proposé dans 13 cas (46,5%), il était à type d'ablation par radiofréquence dans 9 cas (69%) et d'alcoolisation dans 4 cas (31%). Aucune complication majeure du traitement chirurgical ou percutané n'a été notée dans notre étude. La survie globale était significativement plus faible dans le groupe résection chirurgicale. Les survies globales à 6 mois et 1 an pour le groupe résection chirurgicale et le groupe traitement percutané étaient respectivement de 100%, 100%, 20% et 52% ($p = 0,04$). La survie sans récurrence, était comparable entre les deux groupes.

Conclusion: Nos résultats prouvent l'efficacité des traitements percutanés (à savoir la radiofréquence ou l'alcoolisation) qui étaient associés à une survie supérieure par rapport au traitement chirurgical (par résection hépatique) chez les patients ayant un petit carcinome hépatocellulaire. Leurs avantages résident sans doute en leur caractère moins invasif et leur faible morbidité.

Mots-clés

Carcinome hépatocellulaire – Chirurgie – Radiofréquence - Alcoolisation - Survie

SUMMARY

Background: Hepatocellular carcinoma is the first liver tumor worldwide. Therefore, it is a matter of debate whether surgical treatment or percutaneous treatment should be preferred for the treatment of patients with small hepatocellular carcinoma.

The aim of our study was to compare the long-term outcome and the survival between surgically and percutaneously treated small hepatocellular carcinomas.

Methods: A retrospective study was performed in the department of hepatology during a period of 2009-2012. The study included all patients carrying small hepatocellular carcinoma which were divided in: group 1 including patients who underwent surgical treatment, and group 2 including patients who underwent percutaneous treatment.

Results: Among the 63 patients who were diagnosed for hepatocellular carcinoma, 28 carried a small hepatocellular carcinoma with a mean age of 63 years and sex-ratio of 0.64. Etiology of cirrhosis was viral in 96% cases. Surgical treatment (hepatic resection) was performed in 53.5% cases while percutaneous treatment was proposed for 46.5%: radiofrequency ablation in 69% and alcoholic injection in 31%. No major complications for both surgical and percutaneous treatment occurred in our study. Overall survival was significantly lower in the surgical resection group. The corresponding 6 months and 1-year overall survival rates for the surgical resection group and the percutaneous treatment group were 100%, 100%, 20%, and 52%, respectively ($p=0,04$). The disease free survival were not significantly different.

Conclusion: Our results showed the efficacy and safety of percutaneous ablation treatments which were better than those of surgical treatment in patients with small hepatocellular carcinoma.

Key- words

Liver cancer – Surgery - Radiofrequency ablation - Alcoholic injection - Survival

Liver cancer is the sixth most common cancer (749,000 new cases), the third cause of cancer related death (692,000 cases), and accounts for 7% of all cancers [1]. Hepatocellular carcinoma (HCC) represents more than 90% of primary liver cancers and is a major global health problem [1]. The prognosis of HCC is generally poor despite the fact that the diagnosis is nowadays more frequently performed at an early stage, and this, thanks to echographic screening of cirrhotic patients. Consequently, more tumors are diagnosed in an early or very early stage.

Currently, according to the EASL guidelines (European Association for the Study of the Liver) [2], and according to BCLC classification (Barcelona Clinic Liver Cancer Group) [3], local ablative therapy (percutaneous radiofrequency and alcoholic injection) complete with surgical resection and liver transplantation as primary treatment for small, early and very early stages of HCC.

Various loco-regional therapies are used to treat patients who are not candidates for surgery because of the severity of the underlying liver disease (especially developed portal hypertension) [4]. These therapies included percutaneous radiofrequency thermal ablation (PRFA) and local alcoholic injection. There is actually still debate with regard to whether percutaneous treatment or surgical resection (SR) is the most suitable therapy of small HCC.

In the present study, we conducted a retrospective cohort study to compare the long-term outcome and the survival between surgically and percutaneously treated small hepatocellular carcinomas.

MATERIAL AND METHODS

Type of study

A non-randomized comparative retrospective monocentric study was performed in the department of hepatology of Mongi Slim hospital during a period of three years (2009-2012).

Patients

Between 2009 and 2012, within the 63 patients who were diagnosed for hepatocellular carcinoma, 28 patients with single HCC ≤ 5 cm or less than 3 nodules less than 3cm in diameter received curative treatment using surgical treatment or percutaneous treatment in the department of Hepato-Gastro-enterology of Mongi Slim Hospital. Before performing either percutaneous or surgical treatment, a multidisciplinary discussion was made between surgeons, radiologists and gastro-enterologists to decide whether treatment was the most indicated for each patient. Patients with a follow up lower than 6 months were excluded from the study.

The present study comprised a retrospective analysis of patient records. The primary end point was overall survival and the secondary end point was cumulative recurrence free survival.

HCC diagnosis

HCC was suspected by abdominal ultrasound sometimes associated with a high alpha-feto-protein level and confirmed by either dynamic computed tomography (CT) scans or magnetic imaging resonance (MRI), based on the recommendations of the American Association for the Study of Liver Diseases [5], i.e. contrast uptake in the arterial phase and washout in the venous/late phase. Arterial and portal phase dynamic CT images were obtained at approximately 30s and 120s,

respectively, after the injection of the contrast material. Abdominal angiography combined with CT (angio-CT) assistance was performed on all patients before PRFA and SR.

Then, according to the Milan criterias [6], the diagnosis of small HCC (presence of single HCC ≤ 5 cm or less to three nodules ≤ 3 cm in diameter with no vascular invasion and no metastatic invasion using computed tomography) was confirmed.

Percutaneous treatment procedure

1- Radiofrequency

A cool-tip needle was generally used while performing percutaneous radiofrequency. Using the intercostal or subcostal approach, the needle was inserted under real-time ultrasound or computed tomography guidance. The initial treatment was planned with one ablation for tumors of < 2 cm in diameter, and two or more ablations with the overlapping technique for tumors of ≥ 2 cm in diameter. After insertion of the electrode into the tumor, ablation was begun at 60 W for the 3-cm exposed tip and 40 W for the 2-cm exposed tip. The power was increased to 120 W at a rate of 10 W/min. The duration of a single ablation was 12 min for the 3-cm electrode and 6 min for the 2-cm electrode. The procedure was performed under general anesthesia. When tumor ablation was complete, thermal ablation was performed along the needle track. All patients were carefully observed during 24 hours after procedure in order to screen treatment-related complications.

All procedures were performed under ultrasound or computed tomography guidance by experimented radiologists with at least 10 years of experience.

Complete radiofrequency ablation was defined as an area equal to or larger than the ablated tumor without contrast enhancement after single or multiple sessions of radiofrequency procedures in three months.

2- Local alcoholic injection

Split injection of few pure alcoholic solutions was performed thanks to a needle of 19 gauges. Using the intercostal or subcostal approach, the needle was inserted under real-time ultrasound or computed tomography guidance. Absolute alcohol was injected into the tumor at one or more location in one treatment session and the injection was performed two or three times (volume depending to the evaluation of the radiologist) until the total of the injected ethanol reached the volume intended. A safety margin of 0,5cm was considered to be associated with an efficient procedure. The number and the volume of injections were modified depending on the patient compliance, the number of lesions, the location of lesions, the findings of computed tomography with contrast enhancement after therapy and the goal of treatment. Response to therapy was evaluated by imaging (computed tomography or magnetic resonance imaging) with an interval of one to six months.

Surgical resection procedure

All procedures were performed by surgeons who had at least 10 years of experience of surgical resection. Surgical resection was carried out under general anesthesia using a right subcostal incision with a midline extension. We performed anatomic partial hepatectomy with a resection margin of at least 1 cm over the tumor, based on intra-operative ultrasonography guidance which was routinely performed in

order to estimate the location, size, number and feeding vessels of the tumor, as well as to give an exact vascular map of liver anatomy. Hemostasis was achieved with bipolar electric coagulation and suturing. Patients were systematically admitted to the post operative intensive care unit after surgical treatment. When liver function approached normal and adverse events had disappeared after surgical resection, patient discharge was authorized.

If surgical treatment was performed, resected specimen at surgery, and liver biopsy were systematically histologically analyzed in order to confirm both HCC and cirrhosis diagnosis.

Follow-up

Patients were regularly monitored for recurrences in outpatient clinics every 3 months by physical examination, laboratory tests, and imaging studies. If patients treated by percutaneous radiofrequency ablation or by alcohol injection, imaging studies were performed at 6 weeks, 3 months and every 6 months.

Death occurrence or recurrence of HCC were noted. No patients were lost to follow-up. The follow-up period after the treatment was defined as the interval between the date of the initial treatment and that of the last follow-up.

Local recurrence was defined as recurrences contiguous to resection margins in patients who had undergone hepatectomy, whereas in patients treated with percutaneous ablation, local recurrence was defined as recurrences contiguous to or within the ablated areas.

Statistical analysis

All data were analyzed using SPSS software, version 18.0 (SPSS Inc., Chicago, IL, USA) for Microsoft Windows. Differences between the two groups were analyzed using the unpaired t-test for continuous variables, and the categorical variables were analyzed using the khi-2 test. The overall survival curves and the recurrence-free survival curves were generated using the Kaplan-Meier method and compared using the log-rank test. The relative prognostic significance of the variables in predicting overall survival was assessed using univariate and multivariate Cox regression models. Values of $p < 0.05$ were considered to be statistically significant.

RESULTS

Among sixty tree patients presenting HCC, 28 were classified according to BCLC classification as very early stage and early stage and were enrolled in our study.

Among included patients, 15 underwent surgical resection (53.5%) and 13 underwent percutaneous treatment (46.5%). The percutaneous treatment was based on radiofrequency in 9 cases (69%) and alcohol injection in 4 cases (31%).

The median follow-up period was 13.7 months [3-40 months]. The mean age was 63 years [54-84 years] and the sex ratio 0.64 [M/F = 11/17]. Etiology of cirrhosis was viral, corresponding to hepatitis B or C in most cases (96%). Child Pugh score was respectively A and B in 22 (78.5%) and 6 (21.5%) cases.

Table 1 shows the demographics and clinical characteristics of patients in both surgical resection and percutaneous treatment groups.

No significantly differences were observed between the two groups concerning both epidemiological, clinical, biological parameters and

mean follow up. In surgical resection group, a larger proportion of patients had chronic hepatitis B virus infection with a p value near to signification ($p=0,052$). No major complications occurred during follow up for both groups treated percutaneously and surgically. The surgical resection was a tumorectomy in 7 cases (46%) and a hepatectomy in 8 cases (54%). Histological examination of the surgical specimen confirmed the hepatocellular carcinoma in all the cases and showed a well differentiated tumor in 5 cases (3%), moderate differentiation in 5 cases (33%) and poor differentiation in 5 cases too (33%). The resection margins were good in all cases.

Table 1 : Demographic and clinical characteristics of the patients

Factor	Surgical resection (n=15)	Percutaneous treatment (n=13)	p value
Type of treatment	-	Radiofrequency (n=9) Alcohol injection (n=4)	0,630
Median follow up (months)	14,5	12,5	0,380
Male (n=)	5 (33%)	6 (46%)	0,432
Age<60 years (n=)	5 (33%)	4 (30%)	0,052
HBs Ag positive (n=)	7 (46%)	2 (15%)	0,281
Anti-HCV positive (n=)	8 (53%)	11 (84%)	0,221
ALT/AST N (n=)	12 (80%)	6 (46%)	0,328
Mean size (cm)	0,78	0,92	0,6
Child Pugh A (n=)	12 (80%)	10 (87%)	0,454
Ascites (n=)	3 (20%)	4 (30%)	0,321
Alphafoetoprotein > 200ng/L (n=)	8 (53%)	3 (13%)	

In the 15 patients undergoing surgical resection, the 6 and 12 months cumulative survival rates were 100%, and 0%, respectively. The 6 and 12 months cumulative disease free survival rates were 100%, and 65%, respectively. Three patients presented recurrence, within respectively 12, 15 and 15 months. Recurrence of HCC was treated in one case by radiofrequency ablation and in another case by intra-arterial chemoembolization. One patient was treated symptomatically because of the advanced stage of the tumor.

In the 13 patients undergoing percutaneous treatment, the 6 and 12 months cumulative survival rates were 100%, and 50%, respectively. Complete tumor necrosis was obtained with 1 treatment session in the most of cases (69%). The other patients were treated respectively by two (n=3) and three sessions (n=1). There were no recurrence in this group of patients within the follow up period and the cumulative disease free survival was of 100% at 6 and 12 months.

There were significant difference in cumulative survival rates between surgical and percutaneous treatments with a better survival in the percutaneous group ($p = 0.04$) (Fig. 1).

Otherwise, patients who underwent percutaneous resection had significantly better disease free survival rates than those who underwent surgical resection ($p = 0.001$) (Fig. 2).

In univariate analysis predictive factors of survival for early HCC treated by either percutaneous or surgical treatment in our study were age lower than 60 years and normal level of serum aspartate aminotransferase (AST). There was no statistical difference concerning sex, etiology of cirrhosis (viral B or C), alpha-foetoprotein

level, alanine aminotransferase (ALT), alkaline phosphatase level (APL), Child Pugh score (A or B), and tumor size. No predictive factor was objectified in multivariate analysis.

Figure 1 :Survival curves of early hepatocellular carcinoma that underwent curative treatment

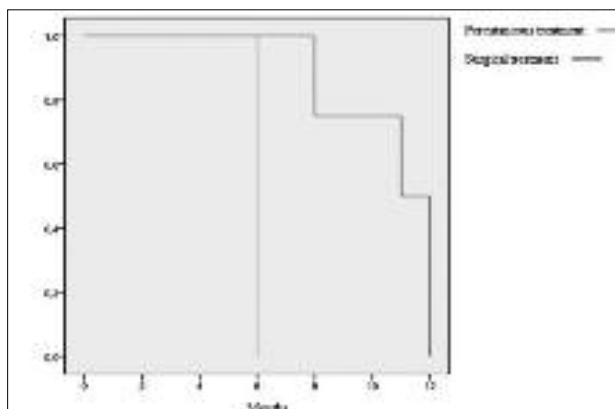
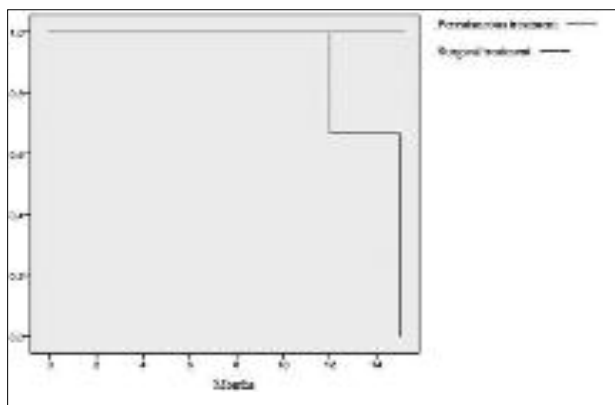


Figure 2 : Free disease curves of early hepatocellular carcinoma that underwent curative treatment



In univariate analysis predictive factors of recurrence for early HCC treated by either percutaneous or surgical treatment in our study were age superior to 60 years and elevated alkaline phosphatase level. There was no statistical difference concerning sex, etiology of cirrhosis (viral B or C), alpha-foetoprotein level, AST and ALT levels, Child Pugh score (A or B), and tumor size.

Alkaline phosphatase level was confirmed as an independent factor of recurrence in multivariate analysis. Predictive factors of survey and recurrence are resumed in table 2.

DISCUSSION

Our study confirmed the efficiency of both percutaneous treatments and surgical resection for the treatment of early HCC. Indeed, it also plaid for a better response to percutaneous treatments with a lower recurrence rate and a better overall survival at 6 and 12 months.

Liver transplantation is known to be the best treatment for patients with HCC who met Milan criteria. However, organ shortage and long waiting time, especially in our country make it as a difficult initial treatment for HCC [7]. Thus, surgical resection and percutaneous treatments are the main treatment options for small HCC patients. Whether surgical resection or percutaneous treatment should be the first-line treatment for these patients is a matter of debate due to the lack of prospective randomized clinical trials. In clinical practice, multidisciplinary decision involving gastroenterologists, radiologists and surgeons to optimize the best treatment is performed. This decision takes into account demographics, tumor status, liver function reserve, etiologies of cirrhosis, and co morbidities of patients. Selecting the correct treatment modality to suit individual patients with HCC remains actually a matter of debate [8]. This prompted us to conduct the current study, which has revealed that percutaneous provided better outcomes for patients with small HCC than surgical treatment.

Surgical resection has traditionally been recommended as the first-line treatment option for patients with small solitary HCC. The 5-year overall survival rate for small HCC ranges from 60% to 100% depending on studies [9]. However, 5-year recurrence rate is elevated, reaching in some studies from 40 to 74.8% [9]. With percutaneous treatment, the 5-year overall survival rate ranges from 55% to 77.8% and the 5-year recurrence rate from 54.8% to 80% [10].

Table 2 : Predictive factors of survey and of recurrence of small HCC after percutaneous or surgical treatment

Factor	Survival			Recurrence		
	Yes (n=23)	No (n=5)	p value	Yes(n=3)	No(n=25)	p value
Male (n=)	8	3	0,290	1	7	0,644
Age<60 years (n=)	9	0	0,01	3	6	0,022
Etiology						
• HBs Ag positive (n=)	7	2	0,553	1	8	0,564
• Anti-HCV positive (n=)	16	3	0,343	2	17	0,430
ALT (U/L)	75	60	0,538	52	75	0,454
AST (U/L)	73	149	0,046	35	90	0,304
PAL (U/L)	414	199	0,252	1469	202	0,05
Alpha-foeto-protein > 200ng/L (n=)	6	2	0,412	2	7	0,967
Tumor mean size (cm)	0,86	0,8	0,157	1	0,84	0,721
Child Pugh score						
• A (n=)	19	3	0,388	3	19	0,470
• B (n=)	4	2	0,285	0	4	0,276

Partial hepatectomy in patients with resectable HCC, who have normal liver function and are in good general condition is still considered the gold standard therapy with the aim of delivering curability [11]. In our study, female patients enjoyed more curative therapy than male regardless of the type of treatment. In recent years, it has been possible to reduce perioperative mortality to less than 5% depending on the extent of resection and hepatic reserve [12]. The improved outcome is primarily as a result of advances in surgical and radiologic techniques, peri-operative care and more cautious patient selection [13]. Patients not eligible for resection because of their medical condition might be candidates for local ablative therapy, such as percutaneous ethanol injection or radiofrequency ablation.

Many clinical trials comparing radiofrequency and percutaneous ethanol injection have demonstrated the clear superiority of radiofrequency [14]. However, a major limitation of radiofrequency is the small volume of tumor that can be treated. There is general consensus that complete response to radiofrequency therapy in patients is associated with improved outcome [15].

However, in our study, with regard to recurrence free survival, there was no significant difference between the two percutaneous treatment groups.

Concerning the comparison of surgical and percutaneous treatment, our result is different from the conclusion made by Hung et al [9] or Livraghi et al [10]. In Hung's study, comparable overall survival and recurrence rates were obtained between surgical resection and percutaneous treatment. Also, in a cohort of patients with potentially operable HCC, Livraghi et al demonstrated that percutaneous treatment yielded 5-year overall survival and disease free survival rates of 68% and 20%, respectively. Despite the good sustained complete response rate obtained by percutaneous treatment, the overall survival and the disease free survival were inferior to surgically treated group.

The findings of the present study indicated that the overall and recurrence free survivals were superior for patients with a small HCC 3 cm treated with either radiofrequency or alcoholic injection compared to surgical treatment. In addition, percutaneous treatment was demonstrated to have an advantage over surgical resection in causing less serious adverse events and a shorter hospitalization length.

Some studies found same results than ours. Chen et al conducted a randomized control trial on 180 patients with a single HCC 5 cm to receive either radiofrequency or surgical resection [11], and Lu et al carried out another randomized control trial on 105 patients with early HCC [12]. These two randomized control trials presented similar findings to those of our study showing the superiority of percutaneous treatment. Additionally, a non-randomized controlled study also reported similar findings of ours [13]. And our study suggests that percutaneous treatment is less invasive than surgical resection. Percutaneous treatment has a major role in the treatment of small HCCs because of its convenience, safety, and low costs [14]. With further consideration about the recurrence, mortality, and morbidity, it seems more suitable for small HCCs, particularly when patients have some contraindications for surgery [15]. In clinical practice, therefore, the feasibility of surgical resection as initial treatment should be assessed before percutaneous treatment.

Moreover, in our series, viral marker distribution showed more hepatitis B virus-infected patients in the resection group compared to the

percutaneous treated group. Because of the limited number of patients and relatively short follow-up duration, we could not draw any conclusions about the importance of such patient characteristics. Nevertheless, no other differences between the two groups were found. In short, the significance of viral marker differences clearly needs further study.

Recent evidence suggests that high alpha-fetoprotein levels are associated with both the presence of portal venous invasion and intrahepatic recurrences after the treatment in HCC [16]. This fact was not confirmed in our study. Otherwise, multivariate analysis has objectified high alkaline phosphatase level as an independent predictive factor of recurrence after HCC treatment. This factor was found in Ueno et al study in 2002 [17].

Tumor size and poor liver reserve has been proved to be important for recurrence and survival [18]. Our analysis also showed that these factors were related neither to recurrence nor to survival. Aged subjects seemed to have more recurrence rates and lower survival in our study. Other factors were found as predictive factors of survival in HCC, including bilirubin level, creatinine level, and platelet count [19,20]. These factors were not objectified as predictive factors of survival or recurrence in our study.

Our study has some limitations. First, it was a retrospective analysis of a small number of patients; second, the follow-up period was low and third, percutaneous ablation therapy included two different treatment modalities. This may interfere with the accuracy of results but we believe that these limitations do not significantly influence the outcome of the study, as the marked differences between each group appear to overcome these biases. These problems should be resolved in a future prospective study.

CONCLUSION

With the present results, we conclude that both percutaneous treatments and resection are effective treatments for small HCC. However, percutaneous treatments are associated with a better survival and a lower recurrence rate comparing to surgical resection. Besides resection, percutaneous treatments can also be considered a treatment of choice for small HCCs, especially in patients with poor liver reserve or co morbidity that make them potentially poor surgical candidates. These treatments have the advantage of being cheap, convenient, and safe. With these advantages, percutaneous treatments will still remain a practical modality for treatment of small HCC, especially in developing countries such as Tunisia.

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