MANAGEMENT OF THE HEPATOCELLULAR CARCINOMA

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LA PRISE EN CHARGE DU CARCINOME HÉPATOCELLULAIRE

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RÉSUMÉ

Introduction: Le carcinome hépatocellulaire, est diagnostiqué de plus en plus précocement du fait des progrès en matière d'exploration du foie, permettant une accessibilité au traitement curatif. La prise en charge de ce cancer demeure difficile en Tunisie.

But : Démontrer les difficultés quand à la prise en charge du carcinome hépatocellulaire en Tunisie.

Patients et méthodes: Ont été inclus tous les patients hospitalisés entre janvier 2002 et décembre 2007, au service de gastro-entérologie de l'hôpital Habib Thameur, pour prise en charge d'un carcinome hépatocellulaire ou pour la surveillance d'une cirrhose.

Résultats : Cinquante-sept patients ayant un carcinome hépatocellulaire ont été colligés dans cette étude. Quarante de ces patients, étaient des hommes (70%), avec un âge moyen de 66 ans (extrêmes : 47-90 ans). La cirrhose était post-virale C dans 28 cas. La découverte du carcinome était systématique dans 16 cas. Seul quinze patients avaient bénéficié d'un traitement. La principale cause à l'abstention thérapeutique était le caractère multifocal du carcinome hépatocellulaire. Les complications étaient à type de décompensation d'une cirrhose (n=3), une fièvre (n=3), une thrombose portique (n=1) et une pleurésie (n=1). Conclusion : Malgré les progrès quand aux moyens diagnostiques et thérapeutiques, seul 17.5% de nos patients ayant un carcinome hépatocellulaire étaient traité de manière curative. Un effort supplémentaire quand au diagnostic et à la prise en charge des hépatites virales et le dépistage précoce du carcinome hépatocellulaire est nécessaire.

MOTS-CLÉS

Carcinome hépatocellulaire - Chirurgie – Transplantation hépatique - Radiofréquence - Alcoolisation - Chimioembolisation

SUMMARY

Introduction: The hepatocellular carcinoma, is detected sooner due to the progress of the hepatic ultrasound scan allowing an accessibility to curative treatment. This cancer treatment still remains difficult in Tunisia.

Aim: To show the difficulties in the management of the hepatocellular carcinoma in Tunisia

Patients and methods: Patients hospitalized in the gastroenterology department of Habib Thameur Hospital, from 2002 until 2007, for a cirrhosis follow-up or for a hepatocellular carcinoma treatment were studied retrospectively. The data was summarized by descriptive statistics and analysed with SPSS version 10.

Results: Fifty-seven patients were registered in this study. There were 40 males with an average age of 66 years. The cirrhosis was post-viral C in 28 cases. The discovery of the carcinoma was systematic in 16 cases. Treatment was prescribed in only fifteen patients, in the other patients, treatment was not made because of the multifocal character of the hepatocellular carcinoma. Complications were cirrhosis decompensation (n=3), fever (n=3), portal thrombosis (n=1) and pleurisy (n=1). Conclusion: Regardless of the improvement of diagnostic and therapeutic means, 17.5% of our patients having a hepatocellular carcinoma were subjected to a curative treatment. An additional effort must be unfolded.

KEY-WORDS

Hepatocellular carcinoma – Surgery – Liver transplantation - Radiofrequency ablation – Percutaneous ethanol injection – Chemoembolization

The hepatocellular carcinoma (HCC), a primitive tumor liver, is nowadays detected sooner due to the progress of the hepatic ultrasound scan allowing an accessibility to a curative treatment. However, its prognosis remains reserved (10 % of curative treatment) [1, 2]. The heptocellular carcinoma has been considered as the main cause of death in cirrhotic patients, and has become the fifth most common cancer in the world and the third cause of cancer-related mortality [2]. Surveillance with ultrasonography (US) and alpha fetoprotein in cirrhosis can detect small HCC at an early stage. For early stage patients (single HCC ≤ 5 cm, or ≤ 3 nodules ≤ 3 cm), surgery is considered the first treatment option [3, 4], however, because of accompanying chronic liver disease, many patients with HCC can not undergo surgical resection. As non-surgical treatment, various local ablation therapies such as percutaneous ethanol injection (PEI), or radiofrequency ablation (RFA) have been proposed, and encouraging results of survival rates have been reported [3].

Over the past few years, several methods for thermal tumor destruction through localized heating or freezing, including laser ablation, microwave ablation and cryoablation, have been developed and clinically tested.

The current potential curative treatments are applicable only in a relatively small proportion of asymptomatic early-stage cases. This cancer treatment still remains difficult in Tunisia. The aim of this study was to demonstrate the difficulty in the management of the hepatocellular carcinoma.

PATIENTS AND METHODS

Patients:

It is a retrospective study, from 2002 until 2007, on patients hospitalized at the gastroenterology department of Habib Thameur Hospital, for a cirrhosis follow-up or for a hepatocellular carcinoma treatment. The following parameters were studied: the age, the gender and the etiology of cirrhosis. The Child Pugh score was calculated. The full blood count, the hepatic and renal balance sheet, the albumin, the prothrombin time ratio, the alpha-fetoprotein level were noted. The diagnosis of HCC was made by imaging, including abdominal ultrasound (US) or computed tomography and by the alpha fetoprotein level. The treatment was curative (surgery, PEI and RFA) or palliative (CE). The criteria for treatment with PEI or RFA were as follow: (1) uninodular HCC ≤ 5 cm or 3 nodules ≤ 3 cm; (2) absence of portal vein thrombosis and extra-hepatic metastasis; (3) age < 75 years; (4) liver cirrhosis of Child Pugh A or B and (5) prothrombin time ratio > 50% and platelet count > 75000/µL. The number of nodules and portal vein patency were established by US. The criteria for CE were: Child-Pugh score < 10, life expectancy > 2 months, age between 18 and 76 years, no central nervous system metastasis, normal renal function, platelet count > 75x109/L.

Schedule:

Before each session of PEI the patients underwent a complete abdominal US examination. After skin disinfection, absolute sterile ethanol (96%) was injected transcutaneously into the tumor using a 0.7 mm needle. Starting at the most distal part of the tumor, ethanol was continuously injected while carefully retracting the needle until the tumor echogenicity became homogenous. After complete ethanol administration, short-term follow-up US control examinations were performed. Six weeks after therapy, CT scan control examinations were performed. In case of detectable remaining tumor vascularisation (indicating remaining vital tumor tissue), tumor growth or new lesions, further PEI treatment was initiated.

During the RFA, and under CT scan guidance, the electrode was placed at the center of the tumor with the electrode tips a few mm deeper than the posterior tumor margin. Pulsed radiofrequency current was emitted over 12 min per needle electrode insertion, with the generator set to deliver the maximum power in the auto control mode based on the tissue

Table 1: Baseline clinical characteristic of patients with the diagnosis of hepatocellular carcinoma

	Surgery (n=3)	**PEI (n=5)**	**RFA (n=3)**	**CE (n=7)**	**Non treated patients (n=41)**
Mean age (year)	62	62.6	69	65.7	68.5
Sex					
Male	2	5	3	5	27
Female	1	0	0	2	14
Causes of cirrhosis					
Hepatitis B	1	3	0	4	5
Hepatitis C	2	2	3	3	18
Alcohol use	0	0	0	0	2
Child-Pugh score					
A	2	1	1	2	9
B	0	3	2	3	23
C	1	-	-	2	7
Albumin (g/L)	32.33	29.87	25.85	27.02	27.35
Bilirubine (µmol/L)	41	196.25	161	40.6	44
Prothrombin Level (%)	57.6	51.75	67	62.6	51.1
Alpha fetoprotein level (ng/ml)	6.86	140.67	26.06	235.06	13127.62

PEI: Percutaneous Ethanol Injection; RFA: Radiofrequency Ablation; **CE:** Chemoembolization

impedance. Tumor necrosis was considered complete when the non-enhancing RFA lesion covered entirely the lesion.
Before each CE session, a CT scan of the abdomen was performed to show tumor extent, and to check for possible extra hepatic disease. After aortography and a selective mesentericoportography to verify vascular anatomy and the patency of the portal vein, a selective hepaticography was performed using a standard diagnostic catheter. According to tumor vascularisation and distribution a mixture of Cisplatin (50 mg/mÇ), 450 to 900 mg degradable starch micro spheres and 5 to 30 mL Lipiodol© were administered. After complete administration, a control hepaticography was performed to document the arterial perfusion and the reduction of tumor vascularisation.
Abstention was decided if these treatments cannot be applied. Complications were mentioned, and survived period was appreciated.
Statistic study:
The data was summarized by descriptive statistics and analysed with SPSS version 10. Data are shown as mean ± standard deviation (SD). Differences in proportions were analysed by chi-square test; differences in mean quantitative value were analysed by student's t-test. P value less than 0.05 was accepted as statistically significant.

Table 1: Characteristics of the tumor in the treated patients and different complications of the curative and palliative treatment

	Surgery (n=3)	PEI (n=5)	RFA (n=3)	CE (n=7)
Number of tumor				
lesion	2	3	3	5
One	-	2	0	0
Two	-	0	0	2
Three				
Tumor diameter				
Mean (mm)	40	22	28.6	40.2
Tumor diameter ≤ 3 cm	0	5	2	3
Complications	Pleurisy Edemato-ascetic decompensation	Spreeding	IAD	IAD Fever Renal failure Diarrhea HE

IAD: Ictero-ascetic decompensation
HE: Hepatic Encephalopathy

RESULTS:

Fifty-seven patients having a hepatocellular carcinoma were registered in this study. These patients were composed of 40 males, the average age was 66 years in all patients (range: 47-90 years) and 26.8% of the patients had an age below 60 years. The cirrhosis was post-viral C in 28 cases and post-viral B in 13 cases, one patient did not have cirrhose and did not be treated. Child-Pugh score was classified below B 7 in 29.8% of the cases. Right side pain was noticed in 28 cases, ascitis in 17 cases, jaundice in 11 patients, fever in 7 cases, poor general condition in 19 cases. The discovery of the carcinoma was systematic in 16 cases (28%). The alpha-fetoprotein level was > 400ng/l in 54%. The table I summarizes the clinical characteristics of patients with the diagnosis of hepatocellular carcinoma. Fifty patients undertook a tomography which showed 11 patients with tumor less than a 30 mm, 11 between 30-50 mm and 22 with a tumor more than 50 mm. Nodules were located in the left liver in 24 cases, in the right one in 11 cases and were diffuse in 13 patients. Nine patients treated for HCC were infected by the C virus. A curative and palliative treatment were prescribed to fifteen patients. The table II show the characteristics of the tumor in the treated patients and the different complications of the curative and palliative treatment.
Three patients were submitted to a surgical treatment. The left liver was concerned each time and the tumor was less than 50 mm in the 3 cases. Complication were pleurisy and edemato-ascetic decompensation in one case respectively. No one benefit by transplantation.
PEI as a percutaneous procedure was made in 5 patients. The mean number of absolute ethanol sessions was 3.2, with a mean dose of 15.8 cc. Tumor diameter was 22 mm and it was located in the right liver in 2 patients. Complication was a tumor spreading.
RFA was done in 3 patients, with a mean sessions of 2.3. The biggest nodule sized 36 mm and was located in the right liver. This treatment was complicated by an ictero-ascetic decompensation.
CE was realized in 7 patients with the Cisplatine as antimitotic agent and with 1.37 mean sessions. Five patients had one nodule and three had tumor size less than 3 cm. Fever occurs in 3 patients, ictero-ascetic decompensation in 2 cases, renal failure in 2 patients, diarrhea and hepatic encephalopathy in 1 case respectively. These complications occur meanly in the 48 hours after treatment.
The main reason for therapeutic abstention was the multifocal character of the hepatocellular carcinoma (n=17), portal thrombosis (n=5), hemostasis trouble (n=2), ascitis (n=6), age > 70 (n=5). The average follow up was about 13 months. Tomography was performed during the follow up in nine patients, with an average of 12 weeks, and 7 of them made a second tomography in an average of 9 months after the first treatment. Six patients did not have a recurrence of the hepatocellular carcinoma, however 3 patients committed a second offence and 3 developed a metastasis.

COMMENTS

In our study only 26.3% of the HCC patients makes a treatment (curative or palliative), this results demonstrate the difficulty in the management of the HCC. Despite major advances in the screening programmes to diagnose HCC at an early stage, only 30-40% of HCC patients will benefit from effective treatments: surgical resection, liver transplantation, PEI, RFA, CE. Our results are yet less than the literature and the introduction of a better screening programme became urgent.

Cirrhosis is the strongest and the most common known risk factor for hepatocellular carcinoma, particularly cirrhosis related to hepatitis C virus and hepatitis B virus infections [4]. HCC is one of the most serious and common malignancy worldwide. Its management involves multiple disciplines including hepatology, surgery, diagnostic and interventional radiology, oncology, and pathology.

In the treatment of HCC, only 20-30% of patients are candidate for surgery. Thus, various non-surgical therapies, such as PEI and RFA have been widely used for small HCC. Surgery resection could be offered only in patients without extra hepatic metastases [5]. Hepatic resection is the treatment of choice for HCC in non-cirrhotic patients who can recover from resection that preserve at least 2 segments of functional liver [6]. In cirrhotic patients, surgery could be proposed only in case of well-preserved cirrhosis and those who could tolerate resection of up to 2 segments [7]. If a resection of more than 2 segments is necessary, a preoperative portal vein embolization to induce hypertrophy of the remnant liver would be useful. The main prognostic factors after resection are presence of cirrhosis, tumor size, number of tumors, vascular invasion and poor differentiated HCC [4]. In our study only 3 patients was able for a surgical treatment and edemato ascetic decompensation was the main complication.

Liver transplantation, as the second curative surgical treatment, could simultaneously removes the tumor and the underlying cirrhosis thus minimizing the risk of HCC recurrence. The transplantation can be done in patients with a solitary nodule of 5 cm or less or patients with no more than 3 nodules less than 3 cm and no invasion of major blood vessels or lymph nodes [8]. Due to the severe shortage of donor livers, organ allocation to transplantation is justified only if the expected results are comparable to those of patients undergoing liver transplantation for benign disease [9,10]. Using these criteria, the 5-years survival rates arise 70% and the recurrence rates are < 15% [4, 7]. To minimize dropout from the waiting list, the treatment of HCC with procedure such as Chemoembolization, Radiofrequency Ablation or Ethanol Injection in patients awaiting liver transplantation have became widespread [11]. In our series no liver transplantation was made, because of the lack of the liver's donor, and the difficulties for the follow-up.

Minimally invasive percutaneous treatments are the best treatment alternatives for early HCC patients who are not eligible for surgical resection or transplantation. PEI consists of injecting absolute ethanol directly into the HCC lesions [4, 9, 12]. It achieves complete tumor necrosis in 70-80% of solitary HCC ≤ 3 cm and in almost 100% of tumors less than 2 cm. Tumor necrosis is less likely to be achieved in large tumors: more than 90% in small HCC (< 2 cm), 60-70% in 3 cm HCC, and less than 60% if up to 5 cm. The advantages of this technique are: low cost, simplicity, ease of performance, minimal equipment and good tolerability [7]. RFA consist on the produces of thermal injuries via an alternative electric current. This RFA give better local control than PEI, with a higher complete necrosis rate (90.3% by RFA and 80% by PEI, with an average of 1.2 sessions for RFA and 4.8 sessions for PEI). Moreover, recurrence rate, disease free survival, over all survival and risk of local tumor progression are more important in RFA than PEI. The equipment is expensive but the complete necrosis could be obtained in less time than with PEI. So, RFA should be considered for patients with very early stage HCC, when resection cannot be applied and for patients with early stage HCC who are not candidates for liver transplantation and possibly for those with long waiting times > 3 months [8]. However, severe complications arise with RFA, such as hemothorax, intra peritoneal bleeding, liver abscess, liver infraction and diaphragmatic hernia. RFA is difficult with tumors located near the gall bladder, bile ducts and diaphragm [4, 13].

CE involves injection of a cytotoxic drug (usually Doxorubicin, Mitomycin or Cisplatin) mixed with Lipiodol followed by embolization using absorbable particles. This CE offer palliative benefits for patients with intermediate stage HCC who exceed the criteria for liver transplantation, with a 5-year survival rate after treatment exceeding 50%. It improves survival in patients outside the early stage criteria, especially those without cancer-related symptoms or vascular invasion. Its safe and effective use is limited to patients with preserved liver function, absence of extra hepatic spread or vascular invasion and no significant cancer-related symptoms [4, 7, 14]. CE is associated with adverse events in 10% of treated patients this include ischemic cholecystis, nausea, vomiting, bone marrow depression and abdominal pain. A post embolization syndrome is reported in > 50% and include fever, abdominal pain and moderate degree of intestinal obstruction. CE is the only palliative treatment that has been proven to be active. Complications in this study in the chemoembolized patients are more frequent than in the percutaneous treatment.

In addition to the role of radiotherapy (RT) in locally advanced and metastatic HCC, technologic advancements have made RT a potentially curative treatment option for patients with liver-confined HCC [15]. High-dose RT delivery in a variety of fractionations schemes, with and without hepatic arterial chemotherapy or CE, has been used safely in these patients with encouraging results. Outcomes are improved in patients who receive higher doses of RT, and toxicity is related strongly to the uninvolved liver [15,16]. For small tumors (< 5 cm), RT is associated with excellent local control.

Many other palliative therapies have been tested like estrogen blockade, antiandrogens, somatostatin. Besides, there are possible future therapeutic strategies including epidermal growth factor receptor inhibitors, antivascular endothelial growth factor therapies, cyclin D inhibitors and HMG-CoA reductase inhibitors [17]. Merle et al thinks that interferon and

differentiating agents may be a probable agents who could play a key role in modeling liver oncogenesis while they have rather poor efficacy for controlling tumor growth [18].

CONCLUSION

Despite major advances and the implementation of screening programmes to diagnose HCC at an early stage, only 17.5% of our HCC patients were subject to a curative treatment. In the mean time, antiviral approaches that reduce replication or induce persistent eradication of HBV or HCV infection are likely to have a substantial effect on the prevention of hepatocellular carcinoma and should be pursued. Identification of risk factors amenable to intervention should be a high priority in the prevention of HCC. An additional effort must be unfolded for an early detection and an enlargement of indications of the curative and palliative treatment to improve the quality of the attended patient's life.

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