Long-Term Survival of a Patient with a Large Unresectable Hepatocellular Carcinoma: Case Report and Review of the Literature

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Abstract: Amongst therapies for unresectable hepatocellular carcinomas, radiofrequency ablation (RFA) and hepatic artery chemoembolization have clinical application either for local tumor destruction or to control tumor progression and recurrence rate. Herein we present a patient with a large hepatocellular carcinoma, chronic hepatitis B and congenital absence of left hepatic lobe treated with hepatic artery chemoembolization, multiple RFA sessions and transarterial chemoembolizations resulted in long-term survival far beyond actual expected survival rate, while preserving quality of life.

Keywords: Unresectable hepatocellular carcinoma, survival, radiofrequency ablation, chemoembolization.

INTRODUCTION

The incidence of hepatocellular carcinoma (HCC) has risen steadily in the last few decades due mainly to the spread of hepatitis B and C virus infections. For most patients with HCC, curative treatment is limited due to liver dysfunction resulting from chronic inflammation and cirrhosis. Surgical resection is the only treatment proven to increase patient survival [1, 2]. Unfortunately, less than 10-30 % of all patients with hepatic malignancies have resectable disease. Most patients with untreated liver tumors die within 4-6 months of diagnosis. The prognosis depends on the degree of tumor growth and the extent of the liver function disorders. Recurrence is common and is the main cause of later deaths as a result of either intrahepatic metastasis from the primary tumor arising in the remaining liver tissue or, of multicentric occurrence [3, 4].

Patients with unresectable disease may be candidates for other treatments including, local ablative techniques, such as radiofrequency ablation (RFA), hepatic artery transcatheter chemotherapy and chemoembolization (HACE), transarterial chemoembolization (TACE), systemic chemotherapy, hormonotherapy and immunotherapy.

RFA is widely used for patients with unresectable primary and metastatic hepatic tumors. The RFA procedure can be performed either operatively *via* laparotomy or laparoscopy or, in a radiology suite *via* a percutaneous approach [5]. The efficacy of RFA treatment is dependent on the size of the tumor. For small tumors (< 3 cm), RFA treatment can reach over 90% local control of lesion with complete necrosis [6]. Tumors larger than 5 cm have lower percentages of complete necrosis and a higher rate of recurrence, thus multiple placements of needle electrode may be necessary to completely destroy the tumor. Independent recurrence risk factors after RF ablation are, hepatitis B or C infection, multifocal tumor and a high pretreatment alpha-fetoprotein level [7].

Hepatic artery chemoembolization (HACE) was initially developed as an alternative treatment for unresectable non-disseminated liver tumors [8]. HACE has proved to be potentially more effective than systemic chemotherapy, intra-arterial chemotherapy with embolization and mechanical embolization [9]. Some investigators reported that HACE in patients with borderline resectable tumors caused sufficient tumor shrinkage to allow resection [8].

Transarterial chemoembolization (TACE) is a procedure involving the injection of lipiodol and chemotherapeutic agents into the hepatic artery feeding the tumor, by an angiographic technique followed by embolization with gelatin, gelfoam particles, or emulsion of biospheres. TACE represents another therapeutic option for large unresectable liver tumors and has been shown to reduce tumor size and unresectable HCC to become resectable [7].

A case is herein reported of long-term survival (23 months) with good quality of life of a patient with a large unresectable HCC, chronic hepatitis B and congenital absence of left hepatic lobe, treated with RFA and chemoembolization. The management of this patient was a challenge and his survival time far outlasted actual expected survival rate.

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CASE REPORT

A 68-year old male with chronic hepatitis B was admitted to hospital complaining of dull upper right quadrant abdominal ache with mild symptoms of anorexia and nausea. Liver function tests revealed elevated alkaline phosphatase and gamma-glutamyl transferase. The rest of the biochemistry tests, including total bilirubin, alanine aminotransferase, aspartate aminotransferase, albumin, total protein, coagulation profile, urea and creatinine were normal. Serum alpha-fetoprotein (AFP) was >600 ng/ml. Abdominal ultrasonography revealed a large lesion in the right lobe of the liver. Computed tomography showed a huge hepatic tumor (7x 6 cm) in segments 7 and 8 that enhanced with contrast medium during the early phase and thereafter showed low-density areas during the late phase (Fig. **1**). The patient underwent CT-guided liver biopsy that confirmed primary hepatocellular carcinoma. Staging did not reveal any metastatic lesions. Various treatment options were discussed with the patient and as he had chronic hepatitis B and congenital absence of left hepatic lobe, he was considered unable to withstand a large liver resection. So, it was decided to proceed with hepatic artery chemoembolization (HACE) at first, with the aim of possibly achieving tumor shrinkage that would consequently allow further treatment manipulations, including palliative resection. Following laparotomy a catheter was inserted into the hepatic artery to infuse chemotherapeutic agents through a totally implantable infusion device. The chemotherapy scheme included cisplatin 75 mg/m^2, Doxorubicin 40 mg/m^2, lipiodol (15 ml) and lipofudin (10 ml). A second cycle of transcatheter chemoembolization was performed 6 weeks later. HACE was tolerated very well and no toxicities were observed. AFP decreased without reaching normal levels and CT-scanning showed some reduction of tumor size, which was not satisfactory.

Four months later, the tumor had regrown in size (7.65 x 7 cm), presenting a 3-cm central hypodense area of degeneration. The lesion involved the posterior-lateral hepatic aspect (segments 7 and 8). Percutaneous local RFA under CT-scan guidance was decided upon, because of the large tumor size and its location near the dome of the liver. RFA was performed by an interventional radiologist under local anesthesia and sedation (Fig. **2**). Ablation procedure was performed using a "hook-tip" needle housing 7 retractable curve electrodes of the Model RITA Starburst XLi-Enhanced (RITA Medical Systems, Mountain View, CA). The needle electrodes can be used to ablate an area of tissue that is 4 to 7 cm in diameter.

Multiple placements of needle electrode were necessary to completely destroy the tumor. During RFA application, the appearance and progression of hypodense areas to cystic in the targeted tumor were evaluated by CT-scanning that guided the duration of therapy. Each application lasted an average of 12 minutes. In case of repositioning of RFA electrode directed to a hypodense area of tumor, ablation was achieved in a more flexible duration of 6 to 8 minutes.

Thereafter, the patient underwent CT-scanning investigation 1 month later, to assess evidence of viable tissue and incomplete tumor treatment. Some areas of suspicious viable tumor were detected; therefore the patient was immediately retreated with percutaneous RFA to control residual or recurrent tumor areas. One month after the second RFA treatment, serum AFT was still highly elevated (>600 ng /ml) and the tumor had regrown, so a third percutaneous RFA procedure was carried out using multiple placements in viable tumor areas.

Three months later, the patient was investigated again by CT-scanning that showed the tumor had increased in size (11.5 x 8 cm) invading the diaphragm. Open-surgical RFA

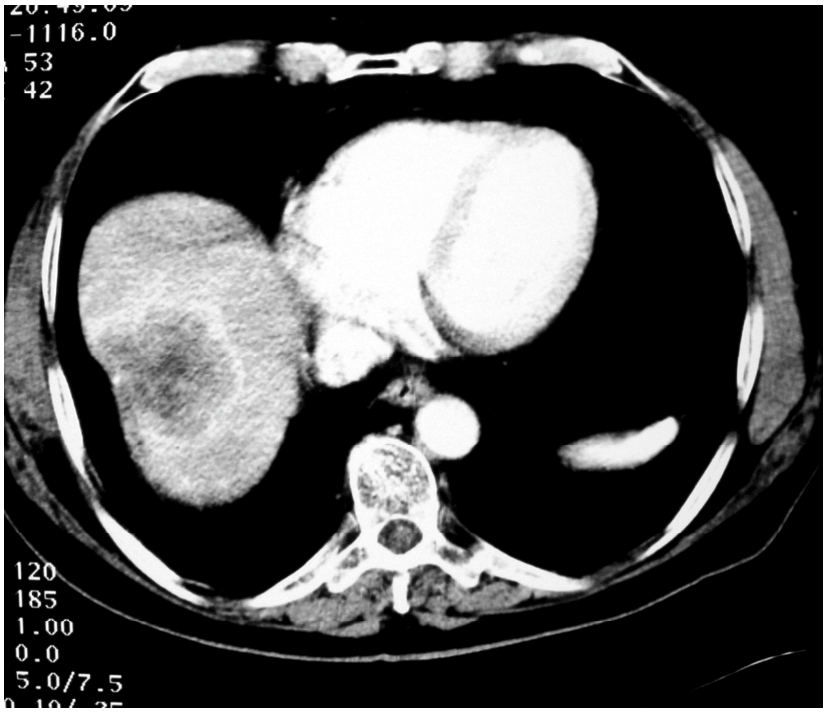

Fig. (1). A single large hepatic lesion (7x6 cm) infiltrating the right lobe of the liver, segments 7 and 8.

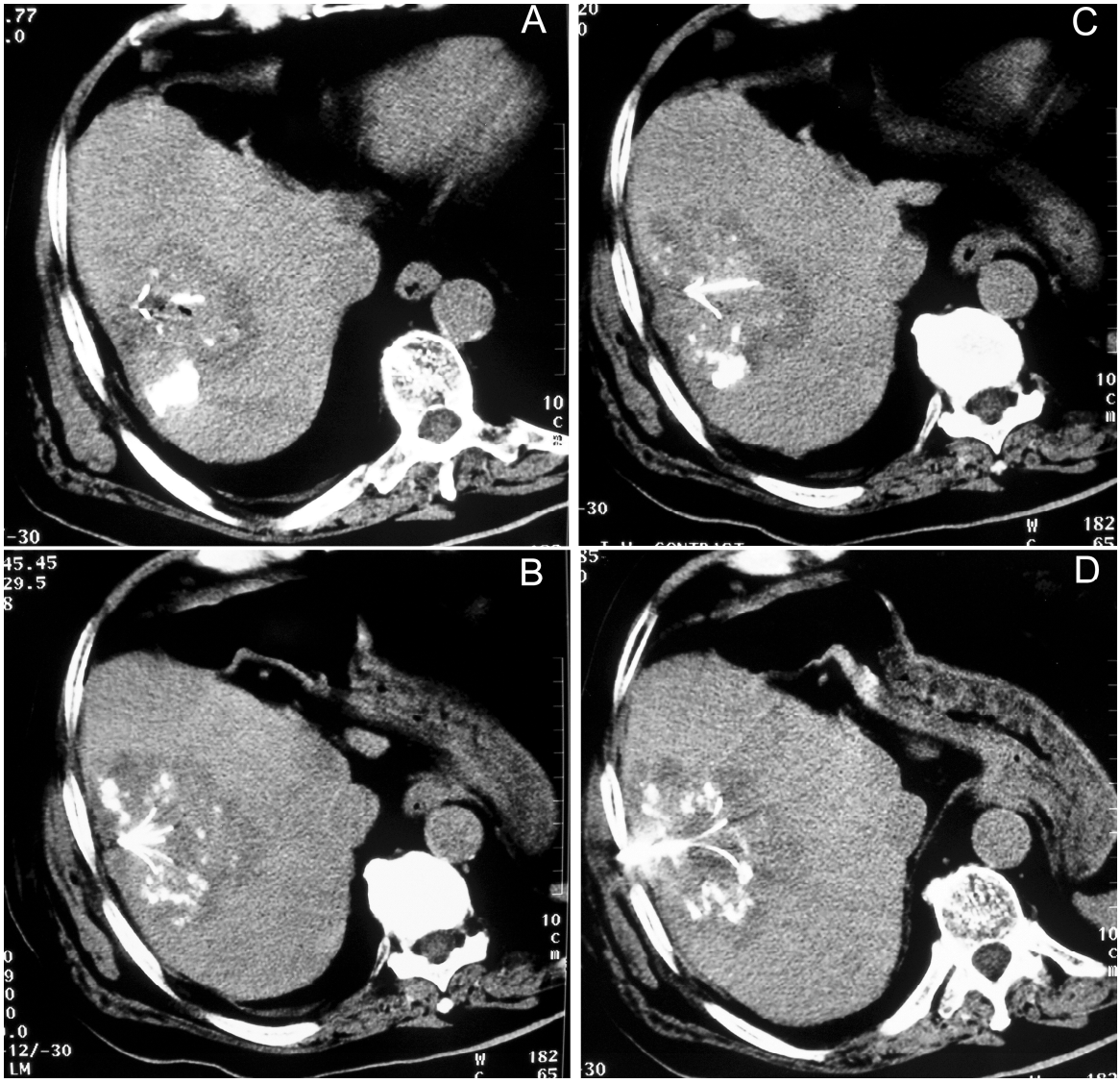

Fig. (2). a,b,c,d: insertion and deployment of the 7 retractable curve electrodes in different positions inside the hepatic lesion under CT guidance. Large necrotic and hypodense areas are illustrated in the targeted tumor.

was decided. During laparotomy the liver was fully mobilized and the huge tumor was dissected free from the diaphragm. Consequently, multiple overlapping ablations (x 9) under ultrasonographic guidance were performed sequentially, starting first from the most posterior interface between the tumor and non-diseased liver parenchyma and then proceeding to the more anterior aspects of tumor. The patient tolerated the procedure well. There was a transient derangement of liver function during the initial postoperative period which had returned to preoperative levels by day 12. He was discharged two weeks after surgery, in relatively good condition and able to carry out his normal activities.

Three months later, the patient repeated spiral CT-scanning that showed evidence of recurrence. Because of the huge tumor size requiring multiple RFA treatments associated with high local recurrence rate, it was considered that transarterial chemoembolization (TACE) would be effective in controlling tumor progression. TACE was performed by selective catheterization of the arterial branch to segment 8 that perfused through collaterals the rest of the tumor. An emulsion of chemotherapeutic agents was infused, including: iodized oil (lipiodol) 15 ml, doxorubicin 40mg/m^2, cisplatin 75 mg/m^2 and an emulsion (4 ml) of biospheres 500-700 μm. A week after TACE procedure the patient developed liver failure associated with hepatic encephalopathy and transient bone marrow suppression. (Ht: 21.6, WBC: 900, PLT: 66000). The symptoms lasted approximately 10 days and gradually reversed. The patient was discharged 2 weeks later, in reasonable condition.

Two months later, a further CT-scan revealed an additional small (2 cm) tumor seeding lesion between the liver capsule of segment 6 and parietal peritoneum (Fig. **3**). Three months later, the patient gradually developed obstructive jaundice and symptoms of chollangitis. A CT-scan showed obstruction of the distal common bile duct due to lymphonode blockage around the hepatoduodenal ligament. The tumor had grown in size (13.5 x 11.0 cm) extending to segments 5 and 6 around the portal vein. An expandable stent was inserted percutaneously through the blockage and in combination with iv antibiotics the symptoms of

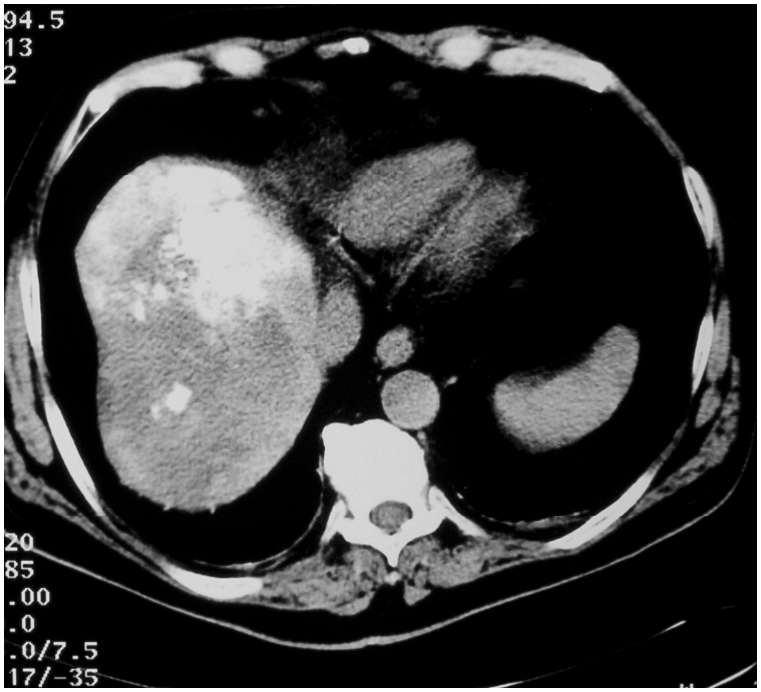

Fig. (3). CT showing tumor regrowth, extending almost to the entire liver parenchyma.

chollangitis were resolved. Hepatic disorders were improved by supportive treatment and 2 weeks later, the patient was discharged with resolving jaundice and in satisfactory condition. The patient passed away 23 months after initial diagnosis. The timeline of the patient's treatment and interventions is shown in Fig. (**4**).

The patient's quality of life was preserved throughout treatment. He suffered no pain or fatigue. He did not exhibit any signs of depression and he maintained his appetite during his treatment. His emotional and social functioning were also maintained.

DISCUSSION AND REVIEW OF THE LITERATURE

The majority of patients with large liver tumors are not suitable candidates for curative resection. Several studies have shown that large lesions (>5 cm) incur a significantly higher risk of recurrence [3, 10]. The management of large unresectable HCC usually requires a combination of treatments because of the high disease progression rate at the intrahepatic site and, of tumor multifocality.

When resection is not possible, the therapeutic options are limited to local tumor-ablative techniques, to regional chemotherapy and/or embolization and to systemic chemotherapy, immunotherapy, hormonotherapy and external or internal targeting radiotherapy. In the case of our patient with a large HCC (7 cm), chronic hepatitis B and congenital absence of the hepatic lobe, the rationale of the patient management and treatment, was to possibly shrink the tumor with more than 1 session of HACE followed by serial sessions of RFA, in an attempt to control tumor progression.

Procedures with the potential to down-stage HCC for secondary resection include TACE [11], combined chemo-

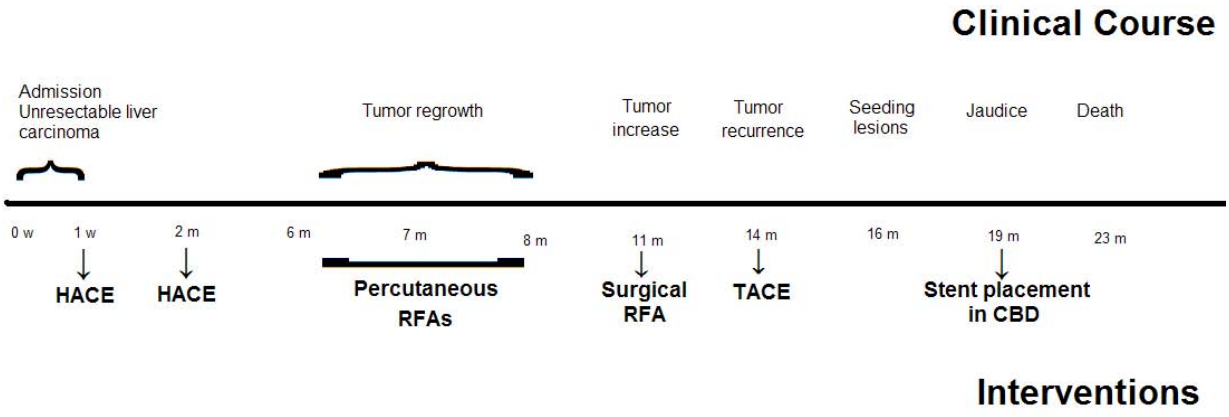

Fig. (4). Time-line of the clinical course and interventions in our patient; HACE=Hepatic artery chemoembolization, RFA=radiofrequency ablation, TACE=transarterial chemoembolization.

therapy and radiation [8], HACE, radioimmunotherapy and embolization [9], transarterial yttrium 90 microspheres [12], systemic chemoimmunotherapy [13], etc. Embolization of portal vein supplying that part of the liver containing the tumor have been seen to reduce tumor size [14]. The main problem with tumor shrinkage is that only a small proportion of patients respond well enough to the treatment to allow secondary liver resection, or other procedure following therapy and, the responders cannot be predicted [8].

HACE has the theoretical advantage of increasing total drug exposure to the tumor, as tumors derive their main blood suply from the hepatic artery. Randomized controlled trials comparing hepatic artery chemotherapy with conventional systemic chemotherapy showed significantly longer survival rate and better quality of life in the hepatic artery chemotherapy group than in those receiving systemic chemotherapy [15]. Other studies showed higher response rate (43%) in the hepatic artery group compared with 9 % in the systemic chemotherapy group and significant increase in the one and two-year survival rates [16]. However, the issue of better effectiveness between hepatic artery transcatheter chemotherapy and systemic chemotherapy in the treatment of unresectable liver tumors has not been resolved. Lipiodol serves as both the targeting agent that carries the cytotoxin agent to the tumor and the embolizing agent that causes blockage of neovasculature of the tumor.

TACE, on the other hand, has been used for many years as a neoadjuvant therapy in an attempt to reduce postoperative recurrence and improve long-term survival. Some clinical studies used TACE preoperatively with the intent of reducing tumor size, to induce tumor necrosis and to prevent tumor cell dissemination during surgery [17]. The effect of preoperative TACE in reducing local and metastatic recurrence and prolonging survival remains controversial [18]. Preoperative TACE results in better disease-free survival if complete tumor necrosis can be achieved, but actually increases the risk of recurrence if only partial necrosis is induced [19]. In addition, the size of HCC at the commencement of chemoembolization is an important prognostic factor in predicting the ultimate response and survival [20]. Complete or massive necrosis after TACE, is seldom observed in HCC larger than 5 cm [21]. Patients with huge lesions have significantly worse survival rates than those with smaller ones, when treated by TACE [22]. Significant complications have been encountered after intra-arterial infusion of chemotherapeutic and embolizing agents involving, gallbladder gangrene, bile duct necrosis, liver infarction, abscess and acute pancreatitis [7]. TACE may also damage the hepatic parenchyma especially in cirrhotic patients, resulting in an increased incidence of liver failure and gastrointestinal bleeding [23].

RFA is an ablative therapy for liver tumors and involves local application of thermal energy producing cellular destruction and tumor necrosis in the form of protein coagulation and dissolution of cell membrane. RFA offers the potential for curative treatment of certain unresectable liver tumors. Clinical trials investigating RFA treatment efficacy followed by resection of malignant liver tumors, confirmed that RFA can create well-circumscribed areas of tumor necrosis with histologic confirmation of cell death [24, 25]. However, clinical data concerning the efficacy of RFA treatment are based on local recurrence rate, overall survival and disease-free survival rates, just as they are for resection of liver lesions. Certainly, patient selection is critical, because most patients with unresectable tumors, candidates for RFA, usually have more advanced tumors with likely subclinical inta-hepatic metastasis.

For patients with small HCC lesions, less than 3 cm, some clinical trials using RFA treatment, showed that 90 % of tumors achieved complete necrosis with treatment failure attributed to improper placement of needle-electrodes [6]. Comparing RFA effectiveness with other local ablative therapies such as, percutaneous ethanol injection and cryotherapy, RFA is superior in terms of the radicality of tumor ablation and lower complication rates [26]. Other clinical trials [6] dealing with solitary, encapsulated HCC lesions, less than 5 cm, in cirrhotic patients awaiting orthotopic liver transplantation, used percutaneous or laparoscopic RFA in an attempt to attain local tumor control and prevent progression. In these series, RFA was proved to be a safe and effective treatment of small HCC (<3 cm), although lesions (> 3 cm) and waiting transplantation time (> 1 year) are associated with high risk of tumor persistence in the targeted nodule. As regards tumor recurrence, it was registered only in patients with HCC >5 cm who had partial response after RFA, while none of the patients with complete necrosis after successful RFA suffered tumor recurrence after liver transplantation.

The therapeutic efficacy of RFA for medium (3.1 –5.0 cm) and large (> 5 cm) HCC lesions is directly related to tumor size and morphology. Clinical trials [5] reported that RFA resulted in complete necrosis, in noninfiltrating medium sized tumors in 71 % of cases and, nearly complete necrosis in 24 %. Complete necrosis was achieved significantly less frequently in large tumors over 5 cm, infiltrating or noninfiltrating. Other investigators [5] reported that approximately one third of RFA ablated large lesions recurred at a median follow-up rate of 9 months and required serial ablations. Larger tumors were successfully ablated with multiple overlapping fields that were performed sequentially, including the lesion and 1-cm margin of normal hepatic parenchyma. As the tumor size increased, the number of overlapping ablations and total application time of RF energy increased.

The accumulated experience of many investigators confirms that local recurrence occurred more frequently in significantly larger lesions ablated by RFA and recommended open-surgical approach for those patients that could tolerate surgery, for more accurate ablation of the entire tumor and the surrounding liver tissue. Additionally, in patients with recurrence or progressive disease, the optimal management usually requires a combination of other treatments hepatically-directed and systemic chemotherapy. So, hepatic artery chemoembolization can be used in these cases, to treat residual tumor, because the hepatic artery is preserved. This is the reason why such a complex therapeutic management of our patient was followed. The most annoying complication of any ablative technique is tumor seeding [27, 28], which can be avoided by performing thermocoagulation of the needle tract while removing the needle [1].

CONCLUSION

In the case of our patient where there was evidence of residual disease after every therapeutic treatment, TACE became the procedure of choice in our therapeutic armamentary, taking into consideration the good general performance of the patient and the good quality of life. Importantly, the patient's ability to conduct a normal life maintained all throughout the treatments and during the whole period of his illness, allowed us to perform several therapeutic manipulations necessary to control the liver tumor and increase patient survival. The overall surgical planning and management of the patient with a combination of treatments from which obtaining optimal beneficial effect of each tried, in conjuction with very close monitoring, resulted in more than doubling the actual patient survival time compared to the expected one.

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