Efficacy and safety of ablative techniques in elderly HCC patients

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BACKGROUND: *This study was conducted to evaluate the efficacy and safety of ablative techniques in elderly patients with hepatocellular carcinoma (HCC).*
METHODS: *From February 2004 to February 2009, 80 elderly patients (age ≥ 70 years) affected by non-resectable HCC were treated with a regional palliative approach, trans-arterial-chemo-embolization and radio-frequency-thermal-ablation (TACE, RFA). Our approach includes a first treatment of TACE and then a control CT plan after a month. A possible following RFA can be performed to ensure a complete necrosis of the lesions, and then a further contrast enhanced CT scan after 2 months. For 60 patients, the first TACE was sufficient to treat the disease at beginning. For 15 patients TACE was followed by RFA, and for 5 patients an RFA was performed directly due to nodule localization.*
Response to TACE is assessed every 2 to 3 months with serial AFP level and TC scan.
RESULTS: *Two patients died for related method's causes (2.5%): liver-renal syndrome (1 patients), and portal thrombosis with irreversible postoperative liver failure (1 patients). A total of 15 patients were lost to follow-up (18.7%): 2 (2.5%) patients had died for non-tumor-related causes, 1 due to a liver transplantation, and 12 (15%) due to failure to attend follow-up visits. All patients developed further localisation, medially after 4 months, and underwent TACE treatment for a mean of another two times. A mean follow up is 36.7 months (1-60) with a mean survival rate of 35.1 months (1-60)*
CONCLUSIONS: *We conclude that, even in over 70-year-olds, TACE and RFA treatment should be employed to completely cure HCC, if liver function and tumor stage are acceptable.*

KEY WORDS: HCC: hepatocellular carcinoma, TACE: trans-arterial-chemo-embolization, RFA: radiofrequency-thermal-ablation.

Background

The incidence of HCC has increased worldwide from 250.000 to 1 million new cases a year. Its incidence has a marked geographical variability, being particularly high in South-East Asia and southern Africa, because of the high prevalence of endemic hepatitis B virus (HBV), and lower in North America and northern Europe. Recently, there has been a rising number of HCC cases in Western countries, because of the sequel of hepatitis C virus (HCV) and alcoholic cirrhosis [1].

The risk of developing HCC is known to be age dependent, and thus there will be an increasing number of elderly patients diagnosed with HCC in the coming years because of the increase in population longevity. Compared with a younger population, elderly patients have significantly more comorbidity, particularly from pulmonary and cardiovascular diseases. Moreover, the therapeutic benefit and the toxicity of cancer treatment

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List of abbreviations
HCC: hepatocellular carcinoma; TACE: trans-arterial-chemo-embolization; RFA: radiofrequency-thermal-ablation; AFP: alpha-fetoprotein; CT: computed tomography; HCV: hepatitis C virus; HBV: hepatitis B virus; AST: aspartate-amino-transferase; ALT: alanine-amino-transferase.

in the elderly are largely unknown, as they have generally been under-represented in clinical trials. Many elderly patients are not receiving optimal cancer treatment, as it is often withheld because of a fear of potential toxicities and perceived minimal survival advantage.[2] Many elderly individuals can be considered clinically "fragile" due to their lifetime accumulation of different diseases, making it possible that HCC treatments are less applicable or less useful in elderly patients than in younger ones [3,4].

Current options for the treatment of HCC include surgical resection, transcatheter arterial embolisation and percutaneous ablation therapy. Although surgical resection is considered the first choice of treatment, it plays a limited role in the treatment of HCC because underlying cirrhosis or multiple lesions often exclude surgery. In fact, although liver ultrasonographies and the monitoring of the Alpha-fetoprotein (AFP) level can be useful in early diagnosis, the majority of these cases are diagnosed at an intermediate or late stage, and only 5-15% are resectable at that point [5].

Elderly patients have a high incidence of comorbid illnesses and are usually considered a high-risk group for major surgery. Ablative techniques have been actively developed in the last few years. These techniques are selective in the site of action and are repeatable. With percutaneous or laparoscopic access it is possible to reduce to a minimum the risk to the patient and significantly shortens hospitalization. Transarterial chemoembolisation (TACE) and Radiofrequency thermal ablation (RFA) may therefore be an acceptable alternative [6-8].

The percutaneous techniques use a direct approach on the hepatic parenchyma or an indirect approach through the branches of the hepatic artery.

TACE consists in the introduction of chemotherapeutic agents (Epirubicine, 10 mg) directly into the lesions through the branches of the hepatic artery and in a selective embolisation of the afferent vessel by Gelfoam particle embolisation. In transcatheter oily chemoembolisation, the cytotoxic agent is injected with Lipiodol into the feeding artery of the tumour. Lipiodol (an oily contrast medium) plays an important role both as a carrier of the anticancer drug and as a diagnostic tool. Lipiodol has a selective affinity for HCC cells, so that it remains selectively in the tumour for a prolonged period, allowing the chemotherapeutic agent to act locally at a high concentration resulting in an ischemic region. TACE was usually repeated as often as necessary at 2 to 3 month intervals until tumour progression is achieved, or until liver intolerance or other severe complications occur. Response to TACE is assessed every 2 to 3 months with serial AFP level and TC scan [9-12].

RFA induces deep thermal injury in hepatic tissue while sparing normal parenchyma. Its basic principle includes generation of high-frequency alternating current which causes ionic agitation and conversion to heat, with subsequent evaporation of intracellular water which leads to irreversible cellular changes, including intracellular protein denaturation, melting of membrane lipid bilayers, and coagulative necrosis of individual tumor cells.[13,14]

For the RFA in all patients we used an umbrella electrode needle (at 9 hooks) and the average duration of the application of the radio-frequency is 11 minutes (minimum 5, maximum 33).

Each ablative method can be considered, case by case, an elective and final therapeutic option or as a bridge to a more radical programme ("bridge to resection" and "bridge to transplantation") [15]. In particular TACE and RFA are valid methods, but both have limits, especially in larger lesions (diameter >3cm). In these cases multimodal treatments are preferred [16-19].

Because the flow of blood increases heat loss and the dispersion of heat can reduce the effectiveness of RFA, a possible way of increasing efficacy is to reduce or to avoid heat loss. The flow to the lesion can be substantially reduced by the embolisation of the artery, a TACE-effect, which has also a strong anti-tumour effect. Therefore, if TACE is done before the RFA, the volume of the coagulative necrosis can be increased, so that it is possible to treat even wider lesions [16-19].

The objective of surveillance must be to decrease disease mortality. There is no general agreement in literature regarding frequency of follow-up controls after disease stabilization. Some authors agree that a contrast-enhanced CT scan control after 6 months is useful, while others authors suggest a CT scan sequence every 30-60 days. In other reports a standard protocol of supervision is presented that includes a contrast- enhanced CT 30 days after the first TACE, followed by a liver function test, the serum alpha-fetoprotein level, a dynamic CT scan every three months or when the serum alpha-fetoprotein level was significantly increased [10,15].

We investigated the feasability of ablative techniques in terms of safety and efficacy in elderly patients [5].

Methods

From February 2004 to February 2009, 128 patients affected by non-resectable HCC were treated with a regional palliative approach. We divided subjects into two groups (those < 70 years and those ≥70 years).

PATIENTS: At the time of recruitment, after receiving a detailed explaination of the nature of the procedure and

TABLE I - *Characteristics of Patients enrolled in the present study*

Pre-treatment Background	
Mean age (years)	75.4 (70-83)
Gender (males/females)	58/22
Aetiology (HCV/HBV/alcohol/other)	63/11/16
Tumour stage	
Tumor multiplicity (single, 2,3, >3)	38/21/10/11
Tumor size (<= 2 cm, 2.1-3 cm, >3,1 cm)	44/24/12
Venous tumor invasion (no/yes)	80/0
Extrahepatic metastasis (non/yes)	80/0
Alfa fetoprotein (ng/ml; <20/10-100/>100)	51/5/24
Liver function	
Class Child-Plugh (A/B/C)	76/4/0
Serum bilirubin level (mg/dl)	1.5±0.4
Serum Albumin level (gr/dl)	3.1±0.3
Prothrombin activity (%)	83±8.4
Serum AST level (U/L)	32±26
Serum ALT level (U/L)	78±57
Previous treatment (no/yes)	69/11

Unless otherwise indicated, data are given as the mean (SD).

possible complications, patients provided their written informed consent prior to enrolment. Diagnosis of HCC was based on radiological findings, Alpha-fetoprotein level and biopsy (when needed) according to the Barcelona criteria [15]. Table I reports the pre-treatment backgrounds of the patients at the beginning of the study.

We considered in this study, a total of 80 elderly patients, 58 males and 22 females, with an average age of 75.4 years (70-83). The aetiology was mostly viral (HCV in 53 patients, HBV in 11, and alcohol or other cause in 16). The most common associated pathology were portal hypertension (34 pt), oesophageal varices of grade F1 (26 pt), ascites (6 pt), hyperammonemic encephalopathy (5pt), diabetes (16 pt), arterial hypertension (18 pt), acute exacerbations of chronic bronchitis (7 pt), gallstone (6 pt), ischemic heart disease (29 pt), severe vasculopathic patients (22 pt), and cerebral cavernoma with hemiparesis (1pt).

Contra-indication to RFA were: lesion size greater than 4 cm, lesion near to vital organs such as gallbladder, stomach and colon, lesion adjacent to a main portal or hepatic vein branches at risk of bleeding, subphrenic lesion not easily accessible, or sub capsular lesion at risk of tumour seeding. Exclusion criteria for intra-arterial treatments of HCC were as follows: extra hepatic tumour spread; ascites not controlled by diuretics, active or recent (4 weeks) gastrointestinal bleeding, encephalopathy, biliary obstruction, severe debilitation, active infection or sepsis, cardio-respiration problems, serum creatinine > 0.2 mg/l, serum bilirubin > 0.3mg/l, haemoglobin level < 8 gr/dl, leucocytes < 2.5x10,000/ml, or platelet count lower than 35,000/mmc.[11]

The patients were studied using a standard diagnostic iter.

– *Laboratory examinations:* hematocrit, white blood cell count, blood coagulation tests, values for hepatic function and a-fetoprotein levels, oncological marker: CEA, and Ca 19.9.

– *Instrumental examinations:* ECG, RX chest, abdominal ultrasound, EGDS, and three-phase spiral CT of the abdomen.

In 16 cases (20%), diagnosis was confirmed by histological examinations (14 biopsy, 1 laparoscopy, and 1 open surgery). The biopsy was not performed on the patients when TC scan were highly indicative of HCC and where the level of AFP was high (>200 mg/ml) in accordance with the Barcelona criteria[15].

We treated an average of 2.5 nodules per patient with a diameter average of 2.8 cm (1-6.5).

At the time of recruitment 21 patients (26.2%) had multifocal lesions (more than 3 lesions at the same lobe or lesions in both lobes) and 59 patients (73.7%) had 1 or maximum 2 nodules in the same lobe.

The hepatic functionality has been carefully evaluated with reference to the Child-Pugh classification. At the beginning of the study, 76 (95%) patients belonged to the A class (score 5-6) and 4 (5%) in the B class (score 7-9).

All patients presented a general contraindication to liver resection.

The levels of the AFP were high in 29 patients, with a value higher that 300 mg/ml in 19 of them. In 75 patients TACE was the first treatment. The other 5 patients, who were already treated with the RFA from other hospitals, were included in the study and treated with TACE first.

The co-morbilities remain clinically stable because not affected by the treatment.

Follow-up

After TACE, patients recovered with about 20 hours of bed rest. After this time, compression of the femoral artery, used as an access for administration of medication, was removed. Every 2 hours for the first 6 hours patients underwent clinical examination (abdominal evaluation and measurements of pulse rate, arterial blood pressure, body temperature and diuresis). Daily routine haematological checks were performed in all patients starting the morning after TACE until discharge, usually 3-5 days after the procedure, in order to evaluate the incidence of side effects and the variation of the hepatic functionality (variation of the Child Class).

One month after TACE, a TC scan without contrast agent was performed to assess tumor response. We also performed dosage of AFP and re-evaluated the Child Class after the first month. After 60 days a contrast enhanced CT was executed. Tumor response to TACE was estimated by evaluating the amount of tumor necrosis on CT follow-up imaging and following the WHO recommendations. The necrosis was considered complete only when there was an homogeneous accumulation of

Lipiodol and there was no enhanced contrast in the arterial phase; massive response if the necrosis was between the 90-99% of the lesions, partial for a necrosis between the 50-89%, and poor for a necrosis lower than 50%.[11] In partial response, we performed an RFA application to complete lesion necrosis. In the patients with a combination treatment CEAT- RFA the treatment interval was 1.5 months. In patients re-treated with TACE, the interval between the first and second treatment was an average of 4 months.
We gave an antibiotic for 3 days after each treatment and mild analgesic and antipyretic in the case of temperature or pain.
The morbidity and mortality, average hospitalisation, treatment response, relapse of the disease, appearance of new nodules, and average survival were evaluated.

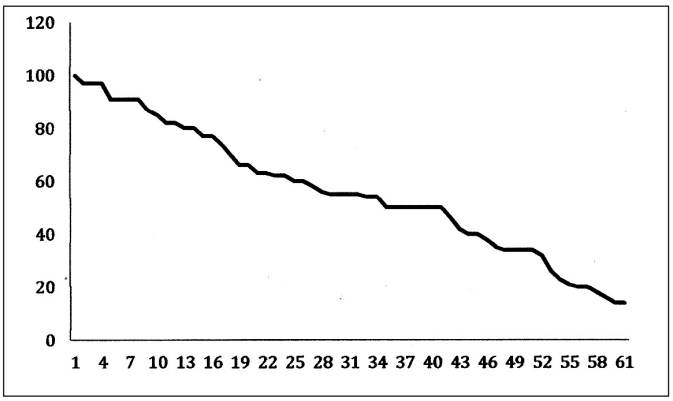

Fig. 1: Survival rates (Kaplan-Meier method): cumulative survival (%) and survival time (mo).

Results

We treated 80 pt. A total of 15 patients were lost to follow-up (18.7%): 2 (2.5%) patients had died for non-tumor-related causes, 1 due to liver transplantation, and 12 (15%) were lost to follow-up visits.
We enrolled patients in a specific protocol. At beginning of the study all patients underwent TACE, and CT scan after 30 days. Sixteen patients also received a RFA, after 2 months. All patients underwent CT scan with contrast medium 3 months after TACE and underwent a second TACE or RFA, depending to vascularisation, localisation and number of lesions, as needed. During our study we performed a total of 131 TACE (all in local anaesthesia) and 39 RFA (7 eco-guided, 25 TC guided, and 7 laparoscopic).
MORTALITY: The mortality related to the methods was 2.5% (2 pt): liver-renal syndrome (1pt), and portal thrombosis with irreversible postoperative liver failure (1 pt). At termination of this study, 26 patients (32.5%) are alive: 14 are stable and 12 were censored due to the worsening of their initial condition resulting in a contra-indication for further treatments.
MORBIDITY: Temperature (t > 37.5 °C) and vomiting appeared in 70% of procedures (30 RFA and 72 TACE) and resolved in 2-7 days with symptomatic therapy. In one patient, there was a hemothorax after the RFA, resolved with drainage; in another a pleural effusion, which was resolved with thoracentesis. A total of 15 patients (18.7%) had urine-retention, for which a bladder catheter was necessary.
Mild analgesic given during procedures was sufficient. The use of antiemetics limited sickness and vomit. Pain was reported in 19 (25%) cases treatmented): described as diffuse abdominal pain or localized to the groin area or right leg after TACE. It was always brief in duration lasting only a few hours and easily controlled with mild analgesic. The average hospitalisation was of 5.5 days (from 2 to 11). The average follow-up was of 36.7 months (1-60), with an average survival level of 35.1 months (1-60) reported by Kaplan-Meyer analysis at Fig. 1).

THERAPEUTIC-EFFECTS: The median survival obtained during this study was 35 months.
Complete necrosis was reached in all the nodules treated. In 60 patients (75%) the first TACE was enough (nodule smaller then 3 cm). The 16 patients, who received the combination treatment (TACE- RFA), for disease residual on the edge of the treated nodule, obtained complete necrosis.
We obtained complete regression in all nodules after only TACE or combined TACE plus RFA, but new lesions or remission of treated lesions were observed after a mean of 4 months. All the patients showed a progression of the disease, usually after a 4-month interval, with new lesions on controlled disease in 57 pt and residual and were re-treated through TACE for an average of twice (1-5 times).
The hepatic functionality showed a characteristic course: it worsened immediately after TACE but normalised after some weeks (usually after three). The RFA had a very small effect on hepatic function. Fifty-five patients (68.7%) maintained the first Child Class (51 A, 4 B), 18 (22.5%) worsen slightly (variation lower than 2 points), 7 (8.7%) worsen heavily (variation around 4 points, from A/B to B/C and from B to C). Stabilisation depended on the relative security of the treatment and on the revision of medical therapy: they were given albumin, lactulose, and amino acid to reduce the amount of ammonium in the blood and to improve general clinical conditions.
The AFP levels were reduced immediately after treatment then increased after some months, usually after three, indicating a. In more than the 50% of patients it remained constant with a value just above average. In three patients it was markedly reduced.
Reduction in stage was obtained in two patients. The first, a 55 year old, was stabilised and enrolled as a can-

didate for a transplant. The second had only one nodule, of the VII segment, with a diameter larger than 7 cm, and excellent hepatic function: after a remarkable reduction of tumor mass, a segmentary resection was performed.

Discussion

HCC patients constitute a particular case in oncology, since their prognosis relies not only on the tumor stage but also on the underlying liver disease. Cirrhosis underlies HCC in most individuals which has a significant influence on outcome simultaneously determining applicability and efficacy of treatments.[12] At the moment of diagnosis, the majority of patients affected by HCC following cirrhosis came to our observation when a surgical approach was not possible [15].

The goal of treatment was the local control of the disease based on the conviction that this will have a positive effect on patient survival compared to just supportive maintenance care. Neither the number of nodules nor their localisation represent a limit, but it is fundamental to treat and render innocuous all discovered nodules. Patients who had the following characteristics were excluded from treatment: presenting with signs of extra-hepatic invasion, that is, infiltration from the hepatic portal vein, lymph node metastasis, wide spread metastasis or heavy hepatic insufficiency (Child C). These conditions are often associated with disease relapse [10,11,17,18].

The advantage of the local ablative methods is the repeatability in time: this permits patient follow up and the treatment of the new injuries that appear during the follow-up, as long as the disease clinically stays at an exclusive hepatic localisation [8].

The RFA has shown to be effective in the treatment of injuries with a diameter of less than 5 cm; the laparoscopic access permits treatment even of injuries near the abdominal wall, near the diaphragm, the intestine and the gallbladder reducing the risk of complications.[14]

Another important advantage of the RFA is to not alter the hepatic functionality of the residual parenchyma. We cannot say the same for the TACE. In fact, it is fundamental to arrive to be as selectively as we can on the afferent vessel at the nodule to close definitively the flow. When the anatomic conditions do not permit this, we use temporary embolisation (Spongostan Gelfoam) nota 18 which allows the initial restoring of the flow after 24 hours and limits the damage at the involved the parenchyma. In this way the pharmacological effect is not limited. The TACE also has the capacity to induce a hypertrophy in the remaining liver, so that it's possible to recover the lost hepatic functionality. Within a few months the patients loose 1 or 2 points of the Child classification [14,17].

In our study we evaluated the improvement of the survival and the achievement of a good quality of life for non-resectable elderly patients treated in a sequential method: TACE followed by RFA. For this reason we elaborated a protocol that permitted us to treat the patients with a standard protocol. The indication at the following treatment was given by the clinical condition of each patient and by the response at the previous treatment.

The achievable effects of the TACE+ RFA treatment are many: the block of the flow in the branching of the hepatic artery increases the necrosis area reachable through the RFA because it eliminates the convection of flow and reduces the impedance in the lesion. Tissue with low impedance suffers more from the heat effect. The destruction of the intra-tumoral septum caused by the mechanical effect of Lipiodol supports the passage of the heat stopping the permanence of saving areas. The RFA acts mostly on the edges of the treated area with the TACE and permits the elimination of the satellite peripheral nodules that resist at the TACE because vascularised by collateral circulation, that are responsible for the relapse of the disease [20,21].

After a shorter or longer period of stability, patients showed a natural progression of the disease that, in our experience, occurs after 4 months, but we were able to locally control disease progression with an average survival of 35 months with a good quality of life.

Most of the complications seen were mild (fever, pain, and encephalopathy) and fundamentally the clinical conditions of the patients did not worsen.

Most of the complications seen were mild (fever, pain, and encephalopathy) and fundamentally the clinical conditions of the patients did not worsen.

The most fearful complication in patients with low hepatic functionality is liver-renal syndrome. This one caused a death at one week from the TACE: the patient started from a Child classification B, the patient had a nodule of 12 cm at the VII segment, for which he had been already treated with more than one cycle of alcoholisation that had a limited efficacy. The selective catheterization of the branch of the hepatic artery afferent to the nodule in the course of TACE proved to be sufficiently smooth to let us embolise in a permanent way the distal part and in a temporary way the proximal part. The patient though rapidly uncompensated and died after the total block of the diuresis.

Another patient went towards a heavy liver insufficiency after two days from the TACE. Through a personalized medical therapy and thanks to the initial good hepatic functionality (Child A), he regained in a week good clinical conditions, so much so that he was discharged 10 days after the treatment. It is clear that the TACE treatment presents a risk of decompensation higher than RFA [8]. We need to evaluate the risks and benefits of these methods.

The average hospitalization was of 5.5 days: this shows how patients can benefit from short hospitalisation with attendant psychological advantages.

The literature to data confirms the superiority of the combined treatment, TACE+ RFA, over single treatment regimes [16]. The best characteristic of these methods is their selectivity of action which makes them repeatable. The local control of disease together with the spearing of the hepatic tissue allows the patient to maintain a good hepatic functionality. It is fundamental also to try to obtain at the beginning of treatment a complete destruction of the lesions. This is possible with the combination of the two methods that have showed a useful complementarily of action [16,19,22-25].

Conclusions

Our results confirm the efficacy of TACE and RFA in elderly patients. The rates of mortality and morbility reported in younger patients are similar to the rate we obtained in over 70-year-old patients.
In conclusion loco-regional treatment for HCC is not dependent on age, although a careful selection of patients is necessary, because both TACE and RFA are effective treatments that can guarantee good local control of disease and the same rate of survival as hepatic resection.

Riassunto

INTRODUZIONE: Questo studio è stato condotto per valutare l'efficacia e la sicurezza delle metodiche ablative nel trattamento dei pazienti anziani affetti da carcinoma epatocellulare (HCC).
METODO: Dal febbraio 2004 a febbraio 2009, 80 pazienti anziani (età ≥ 70 anni) affetti da HCC non resecabile, sono stati trattati con approccio palliativo locoregionale: chemioemolizzazione e radiofrequenza (TACE, RFA). Il nostro protocollo prevedeva un primo trattamento TACE seguito da un controllo TC dopo un mese. Una successiva RFA è stata, eventualmente, realizzata per ottenere una necrosi completa della lesione. Il successivo controllo TC con mezzo di contrasto seguiva dopo 2 mesi.
Per 60 pazienti la prima TACE è stata sufficiente per trattare la lesione inizialmente individuata. Per 15 pazienti la TACE è stata seguita dalla RFA, mentre per 5 pazienti la RFA è stata somministrata dall'inizio per la localizzazione del nodulo.
Le risposte sono state valutate in base alla necrosi del nodulo ottenuta, attraverso la TC, il dosaggio dell'AFP, tempo libero da malattia e sopravvivenza a lungo termine.
RISULTATI: Due pazienti sono deceduti per cause direttamente correlate al trattamento (2,5%): sindrome epatorenale (1 paziente), trombosi portale con insufficienza epatica irreversibile (1 paziente). Quindici pazienti sono stati persi durante il follow-up (18.7%): 2 (2.5%) sono morti per cause non correlate alla neoplasia, 1 dopo trapianto di fegato, e 12 (15%) che hanno mancato i successivi controlli. Tutti i pazienti hanno presentato una localizzazione ulteriore di malattia, mediamente dopo 4 mesi, e sono stati sottoposti a nuovo trattamento TACE per una media di altre due volte. Il follow-up medio è stato di 36.7 mesi (1-60) con un tasso di sopravvivenza media di 35.1 mesi (1-60).
CONCLUSIONE: Concludiamo che, anche nei pazienti anziani, TACE e RFA possono essere impiegati per trattare completamente l'HCC, se la funzionalità epatica e lo stadio tumorale sono accettabili.

References

1) Sherman Morris: *Hepatocellular carcinoma: New and emerging risks.* Digestive and Liver Disease, 2010; 42S: S215-22.

2) Lencioni Riccardo: *Surveillance and early diagnosis of hepatocellular carcinoma.* Digestive and Liver Disease, 2010; 42S: S223-27.

3) Asahina Yasuhiro, Tsuchiya Karou, Tamaki Nobuharu, et al: *Effect of aging on risk for hepatocellular carcinoma in chronic hepatitis C Virus Infection.* Hepatology, 2010; 52: 518-27.

4) Colombo M: *Natural history of hepatocellular carcinoma.* Ann Ital Chir, 2008; 79:91-97.

5) Poon RT, Fan ST, Tsang FH, Wong J: *Locoregional therapies for hepatocellular carcinoma: A critical review from the surgeon's perspective.* Ann Surg, 2002; 235:466-86.

6) Takahashi H, Mizuta T, Kawazoe S, et al: *Efficacy and safety of radiofrequency ablation for elderly hepatocellular carcinoma patients.* Hepatology Research, 2010; 40:997-1005.

7) Mirici-Cappa F, Gramenzi A, Santi V et al: *Treatments for hepatocellular carcinoma in elderly patients are as effective as in younger patients: A 20-year multicenter experience.* Gut, 2010; 59:387-96.

8) Livraghi T: *Radiofrequency ablation, PEIT, and TACE for hepatocellular carcinoma.* J Hepatobiliary Pancreat Surg, 2003; 10:67-76.

9) Xiao-Dong L, Li-Wu L: *Local injection therapy for hepatocellular carcinoma.* Hepatobiliary Pancreat Dis Int, 2006.

10) Riaz A, et al: *Alpha-fetoprotein response after locoregional therapy for hepatocellular carcinoma: Oncologic marker of radiologic response, progression and survival.* Clin Oncol, 2009; 27 (34):5734-42.

11) Miraglia R, et al: *Efficacy of transcatheter embolization/chemoembolization (TAE/TACE) for treatment of single hepatocellular carcinoma.* World J Gastroenterol, 2007 June 7; 13 (21):2952-955.

12) Testa R, Testa E, Giannini E, et al: *Trans-catheter arterial chemoembolization for hepatocellular carcinoma in patients with viral cirrhosis: role of combined staging systems, Cancer Liver Italian Program (CLIP) and Model for End-stage Liver Disease (MELD), in predicting outcome after treatment.* Aliment Pharmacol Ther, 2003; 17:1563-569.

13) Zhou Y, Zhao Y, Yang J, et al: *Meta-analysis of radiofrequency ablation versus hepatic resection for small hepatocellular carcinoma.* BMC Gastroenterology, 2010; 10:78.

14) Curley SA, Izzo F: *Radiorfequency ablation of hepatocellular carcinoma.* Minerva Chir, 2002; 57 (2):165-76.

15) Bruix J, Sherman M, Llovet JM, et al: *Clinical management of*

hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL Conference. Journal of Hepatology, 2001; 35:421-30.

16) Schwartz M, Weintraub J: *Combined transarterial chemoembolization and radiofrequency ablation for hepatocellular carcinoma.* Nat Clin Pract Oncol, 2008; 5 (11):630-31.

17) Bao-Quan C, Chong-Qi J, Chun–Tao L, et al: *Chemoembolization combined with radiofrequency ablation for patient with hepatocellular carcinoma lager than 3 cm: A randomized controlled trial.* JAMA, 2008; 229 (14):1669-677.

18) Wei-Zhu Y, et al: *Combined therapy with trascatheter arterial chemoembilization and percutaneous microwave coaugulation for small hepatocellular carcinoma.* World J Gastroenterol, 2009 February 14; 15 (6):748-52.

19) Kagawa T, Koizumi J, Mine T And The Tokai Rfa Study Group: *Transcatheter arterial chemoembolisation plus radiofrequency ablation therapy for early stage of hepatocellular carcinoma.* Cancer, 2010; 116:3638-44.

20) Sacco R, et al: *Clinical impact of selective transarterial chemoembolization on hepatocellular carcinoma: A cohort study.* World J Gastroenterol, 2009; 15 (15):1843-48.

21) Whoo HY, Jang JW, Choi JY, et al: *Tumour doubling time after initial response to transarterial chemoembolization in patients with hepatocellular carcinoma.* Scand J Gastroenterol, Epub ahead of print.

22) Yau T, Yao J, Tung Pin Poon R, et al: *The outcome of elderly patients with hepatocellular carcinoma treated with transarterial chemoembolisation.* Cancer, 2009; 115:5507-15.

23) Dhanasekaran Renumathy, Khanna Vinit, Kooby David A, et al: *The effectiveness of locoregional therapies versus supportive care in maintaining survival within the Milan criteria in patients with hepatocellular carcinoma.* J Vasc Interv Radiol, 2010; 21:1197-204.

24) Mahady Suzanne E, Charlton Barbara, Fitzgerald Patrick, et al: *Locoregional therapies for hepatocellular carcinoma: which patients are most likely to gain a survival advantage?* Journal of Gastroenterology and Hepatology, 2010; 25:1299-305.

25) Makuuchi M, Donadon M, Torzilli G: *Hepatic resection for hepatocellular carcinoma in cirrhosis.* Ann Ital Chir, 2008; 79:111-116.