

Percutaneous radiofrequency thermal ablation for hepatocellular carcinoma

A. BALDAN*, D. MARINO†, M. DE GIORGIO‡, C. ANGONESE§, U. CILLO¶, A. D'ALESSANDRO**, A. MASOTTO††, M. MASSANI‡‡, M. MAZZUCCOSS, E. MIOLA¶¶, D. NERI¶¶, D. PACCAGNELLA***, G. PIVETTA†††, A. STELLATO‡‡‡, L. TOMMASI§§§, F. TREMOLADA¶¶¶, A. TUFANO****, G. ZANUS¶¶, F. FARINATI* & ON BEHALF OF GENE – GRUPPO EPATOCARCINOMA NORD-EST¹

*Dipartimento di Scienze chirurgiche e Gastroenterologiche, Università di Padova, Padova; †Oncologia Medica, Università di Padova, Padova; ‡Dipartimento di Scienze chirurgiche e Gastroenterologiche, Ospedale di Bergamo; §Medicina Interna, Ospedale di Camposampiero; ¶Clinica Chirurgica I, Università di Padova, Padova; **Medicina Interna, Ospedale di Vicenza; ††Medicina, O.C. Negrar; ‡‡Chirurgia, Ospedale di Treviso; §§Medicina Interna, Ospedale di Este; ¶¶Medicina Interna, Azienda Ospedaliera di Padova, Padova; ***Servizio di Epatologia, Ospedale S. Antonio di Padova, Padova; †††Radiologia, Azienda Ospedaliera di Padova, Padova; ‡‡‡Radiologia, Ospedale di Camposampiero; §§§Medicina Interna, Ospedale di Pordenone; ¶¶¶Medicina Interna, Ospedale di Belluno; ****Medicina Interna, Ospedale di Bassano, Italy

¹See Appendix

Correspondence to:

Dr F. Farinati, Department of Surgical and Gastroenterological Sciences, Padua University, Policlinic, Via Giustiniani 2, 35128 Padova, Italy.
E-mail: fabio.farinati@unipd.it

Publication data

Submitted 15 June 2006
First decision 3 July 2006
Resubmitted 18 August 2006
Accepted 30 August 2006

SUMMARY

Background

Radiofrequency thermal ablation is the first therapeutic option in percutaneous treatment of hepatocellular carcinoma but data on its long-term efficacy and safety are not conclusive.

Aim

This study reports a prospective survey on radiofrequency thermal ablation in north-east Italy.

Methods

Data were collected on 401 patients with hepatocellular carcinoma (males 301, mean age: 68 years) treated by radiofrequency thermal ablation in 13 centres. Indication to treatment was: single nodule not eligible for surgery in 77% of patients, 2–3 nodes in 18% and multiple lesions in 5%. Mean size was 3 cm (1–8 cm). Treatment response was assessed at 1 month by spiral computerized tomography and then with ultrasound examination and new spiral computerized tomography.

Results

Complete response was obtained in 67% of patients and in 27% response was 75–99%. Complete response raised to 77% in lesions smaller than 3 cm. The morbidity rate was 34%; the mortality was 0.5%, seeding was observed in four patients. Ten patients presented an unexpected rapid disease progression.

Conclusion

The above data show that by radiofrequency thermal ablation, complete response can be achieved only in about two-third of the cases, clearly less than expected, and that, beyond seeding, unexpected progression can be observed.

Aliment Pharmacol Ther 24, 1495–1501

INTRODUCTION

Hepatocellular carcinoma (HCC) is a major health problem worldwide, involving 500 000 new cases per year; and in some areas, such as sub-Saharan Africa or China it is the first cause of death due to cancer.¹ Its incidence is increasing in Europe and United States, currently representing the leading cause of death amongst cirrhotics.²

In Western countries, early detection of HCC through surveillance programmes allows so-called 'curative' treatments, such as resection, liver transplantation and percutaneous treatments to be applied in 30–40% of patients.³

Resection and transplantation achieve the best outcome in well selected candidates while, if surgery is precluded, generally because of impaired liver function or portal hypertension,⁴ percutaneous treatments constitute the best option and are considered as minimally invasive and safe procedures, with survival rate similar to surgery.

While up to 5 years ago percutaneous ethanol injection (PEI) was, also from the point of view of the European⁵ and the Italian Society for the Study of the Liver,⁶ the ablation treatment of choice, the last 5 years have seen the progressive spread of radiofrequency thermal ablation (RFTA). This was initially due to the procedure being faster, in terms of number of sessions needed, and to the methodology being more 'scientifically appealing'. Later on however, a number of papers appeared that suggested that RFTA apparently guaranteed higher rates of complete response, lower rates of recurrence and prolonged survival with respect to PEI.^{7–9}

Despite what above, there is no general consensus on whether or not RFTA should replace PEI as the percutaneous treatment of choice in HCC and some scepticism is surfacing,¹⁰ as recent studies^{11–13} have not confirmed the above reports about the efficacy of RFTA and some authors have downsized the enthusiasm by referring a rapid intrahepatic neoplastic progression after treatment.¹⁴

As most of the data published so far derive from the experience of single, highly specialized centres, aim of this study was to assess the effectiveness and safety of RFTA in a survey involving 401 patients with HCC recruited by a multicentric Italian collaborative group [Gruppo Epatocarcinoma Nord-Est (GENE); Hepatocarcinoma (collaborative) North-east (Italy) Group].

MATERIALS AND METHODS

Patients

From 2000 to 2004, 401 patients with HCC were consecutively diagnosed and treatment of RFTA by GENE, in 13 centres. The diagnosis was obtained either by means of fine needle-aspiration biopsy or cytology or on the basis of the standardized EASL criteria for the diagnosis of HCC.⁵

The following criteria were adopted for the choice of RFTA as the treatment option: contraindication for surgery or orthotopic liver transplantation (OLTx), single nodule of 5 cm or smaller or up to three nodules each 3 cm or smaller, Child-Pugh A and B status, absence of portal vein thrombosis or extrahepatic metastases. Before treatment all patients were staged by a spiral, dual-phase computerized tomography (CT) and coagulation parameters were also checked. RFTA was not performed in patients with a platelet count below 40 000/mm³ or prothrombin time lower than 40%.

Techniques

All patients were under deep sedation with propofol plus fentanyl and atropin when required. The procedure was performed under real time ultrasound (US) guidance with a 3.5–3.75 MHz sector probe with a 150 W generator connected to an 14–15 gauge needle with a 2 cm exposed tip (expandable by means of seven or nine hooks – RITA) or by a water-cooled 2–3 cm exposed tip needle (Radionics, Burlington, MA, USA). Treatment lasted an average of 12 min.^{10, 15} Because of tumour size and number of nodules, RFTA was applied a variable number of times in each patient.

Outcome and follow-up

Within 30 days from RFTA, a spiral CT (sCT) was repeated. Complete response rate was defined as no evidence of residual arterial phase enhancement in the treated lesion(s) and no evidence of new lesions.

The subsequent follow-up protocol included clinical assessment, evaluation of liver function by Child-Pugh score, AFP level, US examination, with second-generation contrast media (when feasible) every 3 months and CT scanning every 6 months.

Local recurrence after total necrosis at sCT scan was defined as the appearance of new enhancement areas at the margin or in the centre of the treated lesion.

All cases in which sCT findings were not clear cut; however, reviewed in a centralized manner by the radiologist of the co-ordinating unit and/or re-evaluated by gadolinium-enhanced nuclear magnetic resonance.

Statistical evaluation

The Kaplan–Meier method was used to estimate overall and disease-free survival (DFS). Differences in the survival rates were compared with log-rank test. The overall survival was the interval between starting RFTA treatment and death or last follow-up while DFS was the time interval between the demonstration of absent active disease at sCT 1 month after the first treatment with RFTA and the reappearance of the tumour.

The following variables were considered for univariate and multivariate analysis to identify the risk factors for overall survival:

- 1 participating centre;
- 2 period of treatment (before or after 2001);
- 3 number and diameter of the nodules;
- 4 number of insertions;
- 5 treatment setting (percutaneous laparoscopic/tomic);
- 6 naive patient or retreatment
- 7 complications;
- 8 tumour grading according to Edmonson and Steiner¹⁵ (when the diagnosis was bioptically obtained);
- 9 α -fetoprotein levels;
- 10 patients' age;
- 11 aetiology of liver disease (HCV, HBV, ethanol abuse, others);
- 12 RFTA needle type (RITA, Radionics);
- 13 tumour location (left or right lobe);
- 13 Child–Pugh scoring;
- 14 percentage efficacy of treatment at sCT and
- 15 presence or absence of residual disease.

A *P*-value <0.05 was considered as statistically significant.

RESULTS

Features of patients

From January 2000 to December 2004 we recruited and treated 401 consecutive patients with HCC. The mean age of patients was 68 years, the male/female

ratio was 3/1. All patients were cirrhotic (74% Child A, 26% Child B). Of the above patients, 308 presented with a single nodule (77%), 73 presented with two to three lesions and the remaining 20 (5%) presented a multinodular disease. The diagnosis was supported by histology or cytology in 70% of cases while was obtained according to the EASL criteria in 30%.

About 51% patients had lesions smaller than 3 cm, 38% lesions with a diameter of 3–5 cm and 11% were patients with tumour size exceeding 5 cm, therefore lying outside the original criteria for inclusion.

Radiofrequency thermal ablation was applied only once in 48% of patients, twice in 30% and with multiple insertions in 22% because of tumour size or number of nodules. About 80% of the patients had nodes with a size lower than 5 cm. In these patients median number of needle insertions was 2, with a range of 1–6. All patients with tumour size lower than 3 cm had a single needle insertion. In patients with tumour size exceeding 5 cm (20% of the series) median number of insertions was 3 with a range of 2–4. The application time lasted an average of 12 ± 2.65 min per each insertion. About 7% of the patients were treated by the RITA system and 93% by the Radionics cooled tip needle.

Treatment efficacy and complication

At the CT scanning 63% of nodules presented complete necrosis, in 27% of patients response rate was from 75 to 99%; in 10% of patients lower than 74%. The percentage of total response increased to 67% when, also the results of a second session at brief term, carried out with the aim of completing the treatment, were considered. The highest percentage of complete response rate was observed in patients with single node smaller than 3 cm (77%) while it was 51% in nodules between 3 and 5 cm and only 36% in nodules >5 cm. With respect to efficacy, there was no difference between operators who had performed less or more than 20 RFTA and the percentage of complete necrosis was the same in patients undergoing RFTA before and after 2001, thus suggesting the absence of a learning curve.

About 61% of patients needed additional treatments either immediately or during follow-up because of partial response or disease recurrence. The additional treatments were RFTA in 12% of patients, PEI in 15%, transcatheter arterial embolization (TACE) in 9%, sur-

gery in 5%, medical treatment in 2% and a combination of the above approaches in the remaining. Only about 40% of the patients therefore did not require additional treatments during follow-up.

Procedure-related mortality was 0.25% with a patients dying for complications of colonic perforation. An additional patient had a stroke 20 days after the procedure. The overall incidence of complications was recorded and subgrouped as:

- 1 during treatment (12%);
- 2 during hospital admission (21%) and
- 3 at long-term (following discharge, 6%).

The incidence of major complication during and after treatment was 5%: seven patients developed portal vein thrombosis after discharge. Other major complication reported was seeding (four cases), appearance of artero-venous fistula (one case), intrahepatic abscess (one), subcapsular haematoma (one), haemobilia (one), haemoperitoneum (one) and bowel perforation (one case). The most frequent minor complications were fever and abdominal pain observed in 34% and 61% of patients respectively. We also observed, at the first sCT scanning 1 month after RFTA treatment or within the first 6 months, a rapid intrahepatic progression of disease in 10 cases (2.5%), defined as the unexpected occurrence at short-term of several^{1, 13} new nodules, some times of very large size or of extrahepatic metastasis, with local disease totally ablated or minimal residual disease at first sCT control.

Follow-up

Recently, the mean follow-up is 28 months. The overall survival rate was 85%, 65% and 40% at 12, 24 and 36 months respectively (median survival: 32 months). Survival was longer in patients in Child A risk group, single nodule up to 3 cm (median: 39 months), the differences being statistically significant ($P = 0.01$). No difference in survival was observed when comparing naive vs. pre-treated patients.

Tumour size had a significant impact on survival, patients with largest diameter of ≤ 2 cm surviving significantly longer (62% survival at 5 years) than those with 2–3, 3–5 or >5 cm ($P = 0.001$).

When survival was stratified according to the percentage of residual disease as judged by the radiologists, patients with complete or subcomplete (75–99%) response, had a significantly longer survival than patients with lower response rate ($P = 0.0008$) and the

difference was even more striking when patients with complete response were compared with those harbouring any degree of residual disease ($P = 0.0001$), with a median survival of 48 vs. 31 months.

Multivariate analysis indicated tumour size, efficacy of treatment, Child-Pugh class and presence of residual disease as independent and significant predictors of overall survival. Not significant were the correlations with participating centres, period of treatment (less than or greater than 2001), number of nodules, number of insertions, treatment setting, lack or presence of complications, tumour grading, disease aetiology and needle type. In 50% of patients, cancer recurrence was observed within the first 6 months: 60% of these developed local recurrence and the remaining developed new lesions, distant from the initially treated ones. The overall survival, the survival in patients with residual disease vs. those completely ablated and the DFS rate are illustrated in Figures 1–3. Median DFS was 12 months, 0% at 60 months.

DISCUSSION

When a new treatment is introduced in the clinical practice there is always an enthusiastic phase that is generally acknowledged as the 'honey-moon effect', following which the indications, efficiency and limits of a procedure become clear. In our mind, this is also happening with respect to RFTA. First introduced in 1990s, the first reference paper for RFTA was published in 1995¹⁰ and when the EASL and AISF guidelines of HCC were published, too little evidence was

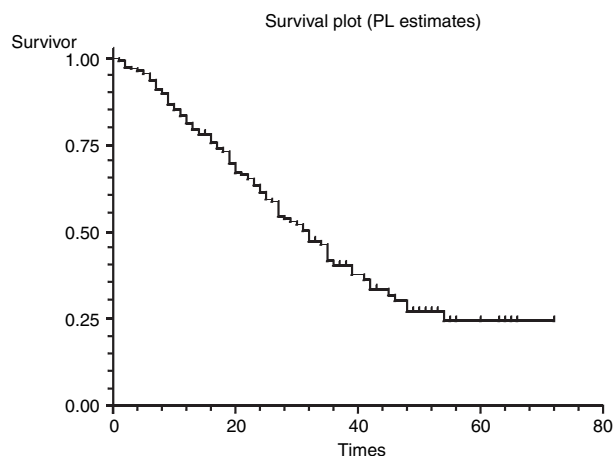


Figure 1. Overall survival.

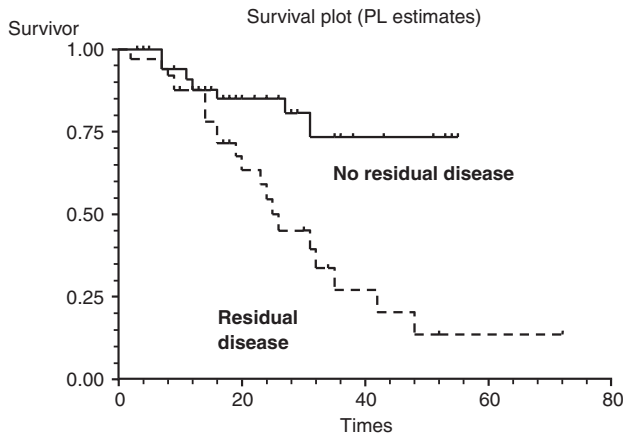


Figure 2. Survival rate in patients with and without residual disease at computerized tomography (CT) scanning. The difference in survival is highly statistically significant ($P = 0.0001$).

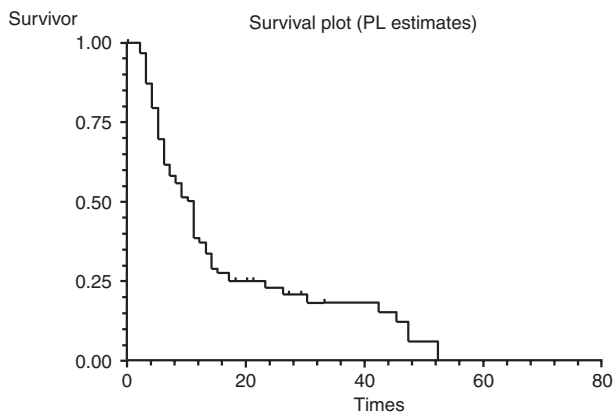


Figure 3. Disease-free survival (0% at 5 years, median: 12 months).

available for declaring RFTA the percutaneous treatment of choice for HCC, this role being still played by PEI. In the following 4–5 years the situations changed and a number of studies^{8,9} were published demonstrating a superiority of RFTA with respect to PEI in total necrosis rate,¹⁶ local recurrence and event-free survival.^{7,17} Some of these studies were not properly randomized prospective-controlled studies and indeed some doubts still persist on the possibility of truly randomizing patients to PEI or RFTA without taking into consideration other variables, such as the position of the nodule. Still the bulk of evidence was in favour of RFTA, with response rates as high as 90–98%.^{18,19}

It remains to be noted that RFTA presents morbidity and mortality rates that are reportedly higher than for PEI,⁷ while the preliminary report recording very high seeding rate has not been confirmed.²⁰

Is all that glitters gold? Perhaps not. Some dissonant voices are now showing that when the gold standard of explanted liver is adopted to assess treatment efficacy, only 46–74% of the patients are successfully treated.^{21,22} The Milan liver transplant group for instance reported a response rate of 55%, with tumour persistence probability increasing with time from treatment, thus suggesting that even patients apparently completely treated have in fact small foci of tumour persistence.²³ Others demonstrate that 3-year survival is much lower than expected from preliminary reports, that figure being 57% at 30 months.²⁴

Overall, almost all authors now agree that when the tumour size exceeds 3 cm the possibility of obtaining complete ablation is relatively low. Given that in nodules characterized by diameter lower than 2 cm PEI is still a reasonable option, as also suggested by the recent Consensus Conference on HCC held in Barcelona, to which the European Association for the Study of Liver Disease, the American Gastroenterological Association and the Japanese Cancer Society took part, this means that in practice RFTA could be only indicated in nodules with size ranging from 2 and 3 cm.

Where do our data stand with respect to the situation described? Overall we support the results more recently obtained. This is based on the fact that:

1 complete response rate with total tumour ablation is obtained in 63% of the cases, a figure that increases to 67% in those who undergo an immediate second RFTA application and to 77% in those with tumour smaller than 3 cm;

2 more than 60% of the patients require additional treatments, such as new RFTA, PEI, transarterial chemoembolization, resection or combined approaches within the relatively short time of follow-up. This is indeed a heavy burden of work, as only in 40% of the patients we can hope to perform a treatment that is 'definitive' within the first 12 months. This is in fact hardly surprising, while surprising were the first reported results, with 2 years recurrence-free survival above 95% (vs. 60% for PEI);

3 morbidity is low but not irrelevant, with 0.25% mortality and a 1% seeding rate;

4 overall survival is 25% at 5 years (with a median survival of 32 months), the figures being 40% for patients with HCC size lower than 3 cm, and 62% sur-

vival at 5 years in patients with tumour smaller than 2 cm and

5 in about 25% of the cases we observed a dramatic and unexpected rapid disease progression, which we already reported,²⁵ with appearance of multiple nodes (up to 13), of large size active lesions (up to 8 cm) or of extrahepatic metastases (lung) at very short-term (1–6 months from treatment) and even in patients in whom complete tumour ablation (at least radiologically) was obtained. This aspect has been so far reported in other three papers^{13, 26, 27} and is, in our mind to appear again if a careful evaluation of the series is performed. A possible explanation is that, under rapid temperature increase and formation of gas within the tumour mass, an ‘explosion’ of the tumour may happen, with dissemination within or outside the liver of neoplastic emboli via portal, hepatic veins or arterial branches. HCC growth may then be boosted by cytokines and growth factors release has been shown in experimental animals.²⁸

Additional observations were the lack of a learning curve, with no difference between units who recruited less or more of 20 cases and between the results obtained earlier or after 2001, this being probably because of the fact that all the centres participating in the study had previous experience with PEI. Also, number of treated lesions, α -fetoprotein levels or tumour grading, patients age, disease aetiology and type of needle had no impact on the results obtained.

The data presented in this study with respect to survival are apparently discouraging but definitely resent of several factors such as:

- the heterogeneity of the patients included and the fact that a substantial share of them had negative prognostic factors, such as lesions over 3 cm in 49% of the cases, 26% of them having a Child-Pugh B risk score and

- probably too low number of insertion in very large-size nodules, in which in any case complete response was pursued by additional treatment strategies.

In conclusion, we agree on the data published by Mazzaferro *et al.*,²³ Cammà *et al.*²⁴ and others that all suggest some caution in evaluating the role of RFTA in HCC treatment, supporting the Barcelona group and Lencioni and Llovet¹⁰ when they state that whether RFTA definitely improves survival in comparison with PEI is still to be defined^{10, 29–31} and the Milan group when they state that RFTA is not to be considered at present an independent therapy for HCC.²³

More aggressive approaches, such as RFTA associated with temporary arterial de-vascularization,³² a more accurate patients selection and/or new advances in the instruments may in future improves the results, but at present we are assisting the end of the honeymoon time and we are waiting to see which the stabilized results will be.

ACKNOWLEDGEMENT

Supported in part by a Grant ‘60%’ by The University of Padua Medical School.

APPENDIX

On Behalf of GENE – GRUPPO EPATOCARCINOMA NORD-EST:

N. Bassi, L. Benvegnù, S. Bergamo, R. Canizzaro, A. Caroli, L. Chemello, M. De Antoni, M. De Boni, S. De Carlo, D. Errante, F. Gaion, P. Inturri, Giordani, G. Mazzarolo, G. Marin, E. Maiolini, C. Manupelli, E. Mastropasqua, M. Molaro, F. Monica, G. Munegato, B. Perin, F. Piccablotto, G. Pozzato, M. Rinaldi, A. Rossanese, M. Ruge, M. Salvagnini, L. Salvagno, M. Santonastaso, P. Tessaro, R. Tumulo, F. Valiante.

REFERENCES

- 1 Parkin DM, Bray F, Ferlay J, Pisani P. Estimating the world cancer burden. *Int J Cancer* 2001; **94**: 153–6.
- 2 San Giovanni A, Del Ninno E, Fasani P, *et al.* Increased survival of cirrhotics patients with hepatocellular carcinoma detected during surveillance. *Gastroenterology* 2004; **126**: 1005–14.
- 3 Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. *Lancet* 2003; **362**: 1907–17.
- 4 Llovet JM, Bru C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. *Semin Liver Dis* 1999; **19**: 329–38.
- 5 Bruix J, Sherman M, Llovet JM, *et al.* Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona – 2000 EASL conference. European Association for the Study of the Liver. *J Hepatol* 2001; **35**: 421–30.
- 6 Bolondi L. (Colombo) *Epatocarcinoma*. Available at: <http://www.webaisf.org/commissioni.htm>. Commissioni e studi conclusi A.I.S.F. – Commissione epatocarcinoma.
- 7 Lin SM, Lin CJ, Lin CC, Hsu CW, Chen YC. Randomised controlled trial com-

- paring percutaneous radiofrequency thermal ablation, percutaneous ethanol injection, and percutaneous acetic acid injection to treat hepatocellular carcinoma of 3 cm or less. *Gut* 2005; 54: 1151–6.
- 8 Lin SM, Lin CJ, Lin CC, Hsu CW, Chen YC. Radiofrequency ablation improves prognosis compared with ethanol injection for hepatocellular carcinoma < or =4 cm. *Gastroenterology* 2004; 127: 1714–23.
 - 9 Llovet JM, Sala M. Non-surgical therapies of hepatocellular carcinoma. *Eur J Gastroenterol Hepatol* 2005; 17: 505–13 (Review).
 - 10 Lencioni R, Llovet JM. Percutaneous ethanol injection for hepatocellular carcinoma: alive or dead? *J Hepatol* 2005; 43: 377–80.
 - 11 Gazelle GS, Goldberg SN, Solbiati L, Livraghi T. Tumour ablation with radiofrequency energy. *Radiology* 2000; 217: 633–46.
 - 12 Francica G, Marone G. Ultrasound guided percutaneous treatment of hepatocellular carcinoma by radiofrequency hyperthermia with a cooled type needle: a preliminary clinical experience. *Eur J Ultrasound* 1999; 9: 145–53.
 - 13 Rossi S, Di Stasi M, Buscarini E, *et al.* Percutaneous radiofrequency interstitial thermal ablation in the treatment of small hepatocellular carcinoma. *Cancer J Sci Am* 1995; 1: 73.
 - 14 Ruzzante A, De Manzoni G, Molfetta M, *et al.* Rapid progression of hepatocellular carcinoma after radiofrequency ablation. *World J Gastroenterol* 2004; 10: 1137–40.
 - 15 Edmonson Ha, Steiner Pe. Primary carcinoma of the liver: a study of 100 cases among 48,900 necropsies. *Cancer* 1954; 7: 462–503.
 - 16 Livraghi T, Goldberg SN, Lazzaroni S, Meloni F, Solbiati L, Gazelle GS. Small hepatocellular carcinoma: treatment with radiofrequency ablation versus ethanol injection. *Radiology* 1998; 230: 1–8.
 - 17 Lencioni RA, Allgaier HP, Cioni D, *et al.* Small hepatocellular carcinoma in cirrhosis: randomized comparison of radio-frequency thermal ablation versus percutaneous ethanol injection. *Radiology* 2003; 228: 235–40.
 - 18 Gaiani S, Celli N, Cecilioni L, Piscaglia F, Bolondi L. Review article: Percutaneous treatment of hepatocellular carcinoma. *Aliment Pharmacol Ther* 2003; 17 (Suppl. 2): 103–10.
 - 19 Lin SM, Lin CJ, Lin CC, Hsu CW, Chen YC. Randomised controlled trial comparing percutaneous radiofrequency thermal ablation, percutaneous ethanol injection, and percutaneous acetic acid injection to treat hepatocellular carcinoma of 3 cm or less. *Gut* 2005; 54: 1151–6.
 - 20 Livraghi T, Lazzaroni S, Meloni F, Solbiati L. Risk of tumour seeding after percutaneous radiofrequency ablation for hepatocellular carcinoma. *Br J Surg* 2005; 92: 856–8.
 - 21 Pompili M, Mirante VG, Rondinara G, *et al.* Percutaneous ablation procedures in cirrhotic patients with hepatocellular carcinoma submitted to liver transplantation: assessment of efficacy at explant analysis and of safety for tumor recurrence. *Liver Transpl* 2005; 11: 1117–26.
 - 22 Lu DS, Yu NC, Raman SS, *et al.* Radiofrequency ablation of hepatocellular carcinoma: treatment success as defined by histologic examination of the explanted liver. *Radiology* 2005; 234: 954–60.
 - 23 Mazzaferro V, Battiston C, Perrone S, *et al.* Radiofrequency ablation of small hepatocellular carcinoma in cirrhotic patients awaiting liver transplantation. A prospective study. *Ann Surg* 2004; 5: 900–9.
 - 24 Cammà C, Di Marco V, Orlando A, *et al.* Treatment of hepatocellular carcinoma in compensated cirrhosis with radiofrequency thermal ablation (RFTA): a prospective study. *J Hepatol* 2005; 42: 535–40.
 - 25 Angonese C, Balcan A, Cillo U, *et al.* Complications of radiofrequency thermal ablation in hepatocellular carcinoma: what about 'explosive' spread? *Gut* 2006; 55: 435–6.
 - 26 Nicoli N, Casaril A, Hilal MA, *et al.* A case of rapid intrahepatic dissemination of hepatocellular carcinoma after radiofrequency thermal ablation. *Am J Surg* 2004; 188: 165–7.
 - 27 Kotoh K, Enjoji M, Arimura E, *et al.* Scattered and rapid intrahepatic recurrences after radio frequency ablation for hepatocellular carcinoma. *World J Gastroenterol* 2005; 11: 6828–32.
 - 28 Ohno T, Kawano K, Yokoyama H, *et al.* Microwave coagulation therapy accelerates growth of cancer in rat liver. *J Hepatol* 2002; 36: 774–9.
 - 29 Llovet JM, Fuster J, Bruix J; Barcelona-Clinic Liver Cancer Group. The Barcelona approach: diagnosis, staging, and treatment of hepatocellular carcinoma. *Liver Transpl* 2004; 10 (2 Suppl. 1): S115–20.
 - 30 Bruix J, Sherman M. Management of hepatocellular carcinoma. *Hepatology* 2005; 42: 1208–36.
 - 31 Lopez PM, Villanueva A, Llovet JM. Systematic review: Evidence-based management of hepatocellular carcinoma – an updated analysis of randomized controlled trials. *Aliment Pharmacol Ther* 2006; 23: 1535–47.
 - 32 Veltri A, Moretto P, Doriguzzi A, Pagano E, Carrara G, Gandini G. Radiofrequency thermal ablation (RFA) after transarterial chemoembolization (TACE) as a combined therapy for unresectable non-early hepatocellular carcinoma (HCC). *Eur Radiol* 2005; 14: 1–9.