Radiofrequency ablation, PEIT, and TACE for hepatocellular carcinoma

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Abstract At detection or over time, hepatocellular carcinoma (HCC) is multicentric in origin, against a background of chronic hepatic disease at different stages. Orthotopic liver transplantation (OLT) is the only therapy able to definitely cure both diseases. When OLT is not feasible, all other options can be only palliative. Owing to the multicentricity, surgical resection may be one possible option at the initial detection in selected patients, whereas percutaneous interventional techniques (percutaneous ethanol injection [PEI], radiofrequency ablation [RFA], selected transcatheter arterial chemoembolization [TACE]) are the options more often used. The range of their indications is becoming wider. Although it is understood that partial resection assures the greatest local control, the survival rates after surgery are roughly comparable with those obtained with PEI. The explanation for this result reflects a balance among the advantages and disadvantages of the two therapies. PEI survival curves are better than curves of resected patients who present with adverse prognostic factors, and this means that a better selection of the patients for surgery is needed. An open question remains the choice among percutaneous techniques. In our department we currently use RFA in most patients but consider PEI and selected TACE complementary, and use them according to the features of the disease and the response.

Key words Liver · Interventional procedures · Liver neoplasms · Therapy · Radiofrequency ablation · Percutaneous ethanol injection · Transcatheter arterial chemoembolization

Introduction

In hepatocellular carcinoma (HCC), as in other tumors, the time of diagnosis governs the type of treatment offered: possibly curative when the diagnosis is early, palliative or nothing when the diagnosis is late. The range of treatment options is fairly wide, and the choice is not always easy, given the number of variables to be assessed. The options open today are: surgery (liver transplantation, partial resection), percutaneous ablation techniques (ethanol injection, thermal ablation, and others), intra-arterial techniques, radiation, and systemic therapies. Most of them have not been validated with randomized controlled studies, for example, versus the natural history or versus other therapies, but are applied only on the basis of the local control of the tumor. The impact on survival of most interventions was measured against historical data. Therefore, selection bias cannot altogether be ruled out.

The survival studies of untreated patients usually taken as points of reference fall into four conventional and gross groups: (1) those relating to patients in whom the disease was at a relatively early stage (single HCC <3 cm or <5 cm, or up to three lesions <3 cm) and therefore likely to be amenable to curative treatment; (2) those relating to patients in whom the disease was considered intermediate, i.e., all the other stages without an invasive tumor pattern (absence of portal thrombosis or extrahepatic spread) and not yet showing symptoms; (3) those relating to patients in whom the disease was considered advanced (between intermediate and terminal stage); and (4) those relating to patients in whom the disease was terminal (performance status [PST] 3–4 or Okuda stage III). A similar staging has been used for practical purposes in many centers but was only recently codified by the Liver Unit of Barcelona and accepted at the Consensus Conference of the European Association for the Study of the Liver (EASL) in 2001. The survival studies on the first group included patients recruited only retrospectively who had not been treated for several reasons. Their 3-year survival ranged between 13% and 21%, reaching 30% in 47 Child class A patients with a single HCC less than 5 cm and deemed potentially operable. The figures
were obtained years ago when imaging examinations were less accurate, so understaging was probable. However, in the future it will be very difficult to carry out a prospective trial considering such patients for ethical reasons, the current availability of no-risk therapeutic options, and the migration of patients. In confirmation of the poor confidence of the aforementioned studies, a surprisingly higher survival rate in 102 patients with an intermediate stage was recently reported. Their 1-, 3-, and 5-year survival was 80%, 50%, and 16%, respectively, with a median survival of 40 months. Such a study was confirmed by a more recent trial which prospectively evaluated 96 patients with an intermediate stage unsuitable for conventional treatments. Their 1-, 3-, and 5-year survival was 72%, 38%, and 20%, respectively. The aforementioned trials opened a debate, because they questioned the previous results of several series of established invasive therapies, such as partial resection or conventional transcatheter arterial chemoembolization (TACE). In fact, the survival of the treated patients was frequently shorter than that of the aforementioned untreated patients, even though the untreated patients had a more adverse profile. For instance, a national study based in Japan demonstrated 1-, 3-, and 5-year survival of 67%, 40%, and 29%, respectively, in 2174 consecutively resected patients. The explanation could be that selection was not strict enough, or also that in some patients potential severe side effects worsened the natural course of the disease.

**Percutaneous interventional techniques**

Percutaneous interventional techniques can be performed using an approach directly through the liver parenchyma or through the hepatic artery. Local ablation therapies are those treatment modalities which allow the introduction of a damaging agent directly into the neoplastic tissue. Local ablation therapies may be based on the use of means capable of destroying the tissue chemically, such as with ethyl alcohol (percutaneous ethanol injection [PEI]) or acetic acid, or physically, as with laser, radiofrequency (RF) or microwave. PEI was the first to be proposed. On the basis of its rationale and the results obtained, the other techniques were subsequently designed. The range of indications for local ablation treatments is becoming wider than that for surgery and intra-arterial therapies. Indeed, whereas for some years only patients with up to three small (<3 or <5 cm) lesions were treated, and this still applies at many centers, with the introduction of “single-session” procedures under general anesthesia, even patients with lesions greater in number or larger in size are now being treated. This article considers only PEI, whose use is the most widespread and codified, and RF ablation (RFA), whose recent results indicate a wide development.

Alcohol acts by diffusion within the cells, which causes immediate dehydration of cytoplasmic proteins, with consequent coagulation necrosis followed by fibrosis, and by entering the circulation, which induces necrosis of endothelial cells and platelet aggregation, with consequent thrombosis of small vessels, followed by ischemia of the neoplastic tissue. Two characteristics of HCC favor the toxic action of ethanol: hypervascularization and the different consistency of neoplastic and cirrhotic tissue. Because the neoplastic tissue of HCC is softer than the surrounding cirrhotic tissue, ethanol diffuses within it easily and selectively, whereas at the same time hypervascularization facilitates its uniform distribution within the rich network of neoplastic vessels. PEI is performed in multiple sessions in an ambulatory regimen (conventional technique) or, when the tumor is more advanced, in a single session with the patient hospitalized and under general anesthesia. The former technique is generally used for a single HCC less than 4–5 cm in diameter or for multiple HCCs with two to three nodules less than 3 cm in diameter. The latter technique is adopted for intermediate HCC, single or multiple, that do not occupy more than 30% of the hepatic volume and with no neoplastic thrombosis in the main portal branches or in the hepatic veins.

The treatment of thermoablation with RF exploits the conversion of the energy of an electromagnetic wave into heat. A generator is used that converts normal energy supplied by an electric alternating current of 90Hz into the RF band of 500 kHz. The current is linked to an active electrode in the form of a needle, which is inserted into the tumor so that the body becomes part of the electric circuit, and the current is dispersed with a resistive type of electrode in the form of a plate, which is applied to the skin of the patient. In this way, a resistive type of heating is produced, particularly around the exposed point of the needle electrode, due to ionic agitation of the tissue electrolytes that follow the change in direction of the alternating current. Heat is generated by means of impedance (resistance) in that the surrounding tissue opposes the flow of current, so that heat is not generated at the tip of the electrode but within the tissue (and from there is also transferred to the electrode). The heat produced is given by the difference between the heat generated around the extremity of the electrode and the dispersed heat, the amount of which depends on the conductivity of the tissue and dissipation by convection due to blood circulation. In the presence of physical and electrical homogeneity, the heat generated around the uninsulated extremity of the electrode is regulated by the distance from the tip, by
Recently proposed, the third device utilizes a cold percutaneous feeding artery occlusion with gelatin sponge particles was hepatic artery occlusion by means of occlusion of the tumor arterial supply, by means of occlusion of the aforementioned techniques, interruption of the tumor arterial supply, by means of occlusion of the feeding arteries with gelatin sponge particles was recently proposed. The third device utilizes a cold perfusion electrode with a diameter of 1.2 mm and the tip exposed for 2–3 cm. By avoiding early increases in impedance linked to carbonization, such electrodes permit the application of greater power than conventional electrodes. To obtain cooling, a physiological solution, brought to 2°–5°C, is circulated within two coaxial lumens situated in the electrode. The technique results in a reproducible area of necrosis about 3–4 cm in diameter. To increase the necrotic area obtained with the aforementioned techniques, interruption of the tumor arterial supply, by means of occlusion of the feeding arteries with gelatin sponge particles was recently proposed. The third device utilizes a cold perfusion electrode with a diameter of 1.2 mm and the tip exposed for 2–3 cm. By avoiding early increases in impedance linked to carbonization, such electrodes permit the application of greater power than conventional electrodes. To obtain cooling, a physiological solution, brought to 2°–5°C, is circulated within two coaxial lumens situated in the electrode. The technique results in a reproducible area of necrosis 2.4 cm in diameter. A recently constructed electrode with three cooled tips, permitting a higher current deposition, results in an area of more than 4.5 cm of coagulation necrosis. Therapy with RFA does not differ substantially from that with PEI as regards the technique of introduction, the investigations, and the parameters used to evaluate therapeutic efficacy, and their timing. At our center, the therapy plan foresees the completion of treatment in only one session, with an eventual retreatment after the first control of therapeutic efficacy. Because the procedure may be painful, it is performed under sedation/analgesia when one or two insertions are foreseen (in lesions <3 cm), or under general anesthesia with tracheal intubation when a greater number is planned.

For many years, transcatheter arterial embolization (TAE) or TACE of the whole liver was the most widely used option for patients with intermediate HCC. The rationale of the approach evolved from the fact that, in contrast with the liver tissue, HCC receives almost the totality of its blood supply through the hepatic artery. TAE and TACE have been confirmed to have a marked antitumoral effect, although only in encapsulated lesions. Surprisingly, three recent controlled randomized trials did not show any statistically significant difference in survival between treated and untreated patients. Treated patients presented a slower tumor progression and even a decrease in the incidence of portal invasion, but the probability of presenting cancer-related complications or liver decompensation was not modified when compared with untreated patients. This is probably due to a counterbalance between local tumor control and damage to non-neoplastic tissue, which hastens liver insufficiency, even though a study particularly dedicated to this problem failed to demonstrate such an interconnection. In the recent study by the Liver Unit of Barcelona, 2- and 4-year survival was 49% and 13% after TAE and 50% and 27% after no treatment. Perhaps further large randomized trials are needed to clarify whether differences in the selection of patients may result in a therapeutic benefit for at least a subgroup of patients. For this reason, the current trend is to use TAE or TACE with a lobar, segmental or subsegmental (selected) technique, which leads to less or no deterioration of liver function than the whole-liver technique, while obtaining a better tumor response.

Rationale

The following points constitute the rationale on which percutaneous interventional procedures are based:

a. They do not have the disadvantage of loss of or important damage to non-neoplastic parenchyma. The underlying chronic hepatic disease, generally of viral origin, accompanies the neoplastic disease in different stages of its course. According to the stage, one disease will prevail over the other. For this reason, therapies should not worsen liver function.

b. They are low-risk procedures. In published series, the mortality rates are insignificant: 0.09% in the largest study of PEI, 0.11% in the largest study of RFA, and no mortality due to selected TAE.

c. They can be easily repeated when new lesions appear, as happens in most patients within 5 years. HCC is considered an organ disease, because it has been proved to be multicentric in origin over time. A recent study demonstrated that multicentricity was already present in 50% of early stages and that 93% of resected patients with a single minute HCC presented other lesions within 5 years. According to the Japanese nationwide survey, only 1.6% of all patients with intrahepatic recurrence were re-resected. Because new lesions reflect the natural history of the disease, the patient should be followed frequently, so that the new lesions can be treated as they form. An advantage is that the patient can be followed by the same physician in the diagnostic as well therapeutic phase.

d. The low cost, easy availability of the necessary material (particularly as regards PEI), and the simplicity of the techniques make it possible to perform them anywhere, even at peripheral centers. Patients with small HCC are generally treated on an outpatient
basis, and most of them can lead a normal daily life. In Italy, the cost of one PEI cycle is about $1000, partial resection about $30000, and OLT about $125000. In Japan, an average cost of $759 for outpatient PEI and $27105 for resection was reported. Because the number of patients who develop the disease every year is about 25000 in Japan and 10000 in Italy, the problem of costs is not of secondary importance.

**Evaluation of therapeutic efficacy**

To evaluate the therapeutic response, that is, to determine whether the tumor has become completely necrotic or whether areas of neoplastic tissue are still present, a combination of investigations and serum assays for tumor markers is used. They are the same as those adopted during initial staging and follow-up. Because there are many investigations and some of them are comparable, we prefer to routinely use only ultrasound (US) with color-Doppler (currently with second-generation echo-enhancers, i.e., SonoVue (Bracco, Milan, Italy) and spiral computed tomography (CT) with the biphasic technique (4–5ml/s, 20 and 60s after the injection of contrast medium). Other examinations or biopsy are performed only in rare cases of doubt about a partial or complete response. If the areas of tissue still viable are very small, beyond the present powers of resolution, they will obviously not be recognizable on the images at the end of the treatment. However, they will be easily identified at successive examinations if they are shown as zones of enhancement on CT or the tumor increases in volume. The response is considered complete when CT scan shows the total disappearance of enhancement within the neoplastic tissue and when the same picture is confirmed at scans performed at successive follow-up. The absence of enhancement means the absence of blood flow due to necrotic and fibrotic modifications. Even with such characteristics, the necrotic area occupies space and remains visible in place of the tumor, but is reduced in size to different extents. Color-Doppler with echo-enhancers can be useful, but it should not be used as the only test to establish the result, because it is less sensitive than CT in showing the vascularity of small viable areas. The different degree of Lipiodol uptake after TAE-TACE is a good indicator of therapeutic efficacy, and its labeling can be easily checked during follow-up by CT scans. As tumor markers, we use alphafetoprotein (AFP) and des-gamma-carboxyprothrombin (DCP), which are often complementary. Nevertheless, their assay is useful only if they are initially high. When the imaging techniques show a complete response not followed by an evident reduction in AFP or DCP levels, it means that neoplastic tissue not detected or not yet detectable is growing elsewhere. Moreover, an increase in levels during follow-up always suggests a local recurrence or the appearance of new lesions. The follow-up with US, CT, and serum assay of tumor markers is carried out a month after treatment and then every 4–6 months.

**Results**

**PEI**

Numerous longterm survival curves have been published in the literature.

A total of 112 patients were treated at the University of Chiba, 93 with one, 16 with two, and 3 with three lesions, all 3 cm or less in diameter. Survival at 1, 3, and 5 years was, respectively, 96%, 72%, and 51% for 60 patients with Child’s A; 90%, 62%, and 48% for 33 with Child’s B; and 94%, 25%, and 0% for 19 patients with Child’s C disease.

Shiina et al. treated 50 patients with single or multiple lesions, with diameters varying from 1.2 to 6.0 cm. Overall survival at 1, 3, and 5 years was, respectively, 87%, 62%, and 43%. Comparison of Child’s A versus Child’s C disease ($P < 0.0001$); diameter, 3 cm or less versus 4 cm or more ($P < 0.0002$); and number, three or less versus four or more ($P < 0.02$), showed significant differences. Lencioni et al. treated 184 patients. A selected group of 70 patients with well-compensated cirrhosis and single HCC 3 cm or less in diameter had 3- and 5-year survival of 89% and 63%, respectively.

A multicenter Italian study enrolled 746 patients. In Child’s A patients ($n = 293$), Child’s B patients ($n = 149$), and Child’s C patients ($n = 20$) with a single HCC less than 5 cm in diameter, survival at 1, 3, and 5 years was, respectively, 98%, 79%, and 47% for Child’s A; 93%, 63%, and 29% for Child’s B; and 64%, 12%, and 0% for Child’s C. In Child’s A patients with multiple HCC ($n = 121$), survival was 94%, 68%, and 36% at 1, 3, and 5 years, respectively.

A multicenter Japanese study enrolled 110 Child’s A patients with HCC 3cm or less in diameter and three or less in number; their 3- and 5-year survival was 83% and 53%, respectively. As regards HCC more than 5 cm in diameter, a study of 108 patients reported the following results: survival at 3 years of patients with encapsulated HCC measuring 5–8.5 cm in diameter was 57%, and that of patients with infiltrating HCC measuring 5–10 cm, or multiple HCCs, was 42%.

In all the aforementioned patients, the main cause of death in Child’s A patients was progression of the neoplastic disease, due mainly to the appearance of new lesions; in Child’s C patients it was hepatic insufficiency.
The incidence of appearance of new lesions at 5 years in the group of patients from the University of Chiba was 87%, in the Shina group 64%, and in the Lencioni group, 78%. In our study, the overall incidence was 87%; 74% in patients with single HCC and 98% in patients with multiple HCCs. The incidence of local recurrences (i.e., local recurrence due to an increase in size or the appearance of viable areas within the lesion treated with PEI) was 4% in the series of Ebara et al.32 (lesions <3 cm in diameter), 7% in the series of Shina et al.33 (lesions ≤4–5 cm in diameter), and 17% in our series (lesions <5 cm in diameter). Many of the recurrences were treated with additional cycles of PEI.

Radiofrequency ablation (RFA)

Theoretically, at the beginning of the experience in humans, the diameter of tissue necrosis was 2.4 cm, the same as that obtained in the liver of animals with the cool-tip exposed for 3 cm.16 Unexpectedly, it was observed that in HCCs 3 cm in diameter, the area and shape of the necrosis reproduced that of the original tumor like a mold. Such an effect was designated an “oven effect”, in that it was believed that the surrounding cirrhotic tissue, because of its high fibrotic component and poor vascularization, was a poor conductor and thus functioned as an insulating material, allowing a higher deposition of energy within the neoplastic tissue.37

A few studies have been published on the treatment of HCC with RFA, only in terms of local therapeutic efficacy.

The first study was carried out using a hooked expandable electrode in 23 patients with HCC up to 3.5 cm in diameter. With an average of 1.4 sessions, a complete response was reported in all the tumors. No complications were observed.88

The second study was a controlled prospective one that compared PEI and RFA in 86 patients with 112 HCCs measuring up to 3 cm in diameter. A complete response was reached in 90.3% with RFA and in 80.0% with PEI. These results were obtained with an average of 1.2 sessions for RFA and 4.8 sessions for PEI. However, there were more complications with RFA, including one severe complication (hemothorax that required drainage) and four minor complications, compared with none with PEI.37

The third study was a prospective one, again comparing PEI and RFA, in 119 patients with single HCC measuring up to 3 cm in diameter. Complete tumor necrosis was achieved in 100% of the RFA group and in 94% of the PEI group, with the same local recurrence rate. RFA required an average of 1.5 sessions, whereas PEI required an average of 4.0 sessions.39

Benefiting from the “oven effect”, a fourth study, on the treatment of larger HCC, was performed.40 In 114 patients with 80 medium (3.0–5.0 cm) or 40 large HCCs (5.1–9.0 cm), complete necrosis was attained in 60 lesions (47.6%) and nearly complete necrosis (90–99%) in 40 lesions (31.7%). Medium and noninfiltrating tumors were successfully treated (71%) significantly more often than large and infiltrating tumors (23%). Two major complications (death of septic shock due to peritonitis in an obese patient with diabetes, and hemorrhage requiring laparotomy) and five minor complications were observed. The results of the study supported the importance of the “oven effect”. However, the “oven effect” may also explain the limited success in treating satellite nodules, which remain a limitation for RF or PEI ablation despite continued technical improvements. Probably, the fibrotic tissue interposed between the main tumor and satellites may limit heat diffusion. A longer follow-up is needed to determine the prognostic improvement which results from treatment of the main tumor alone. However, in some cases, when the location of the satellites is favorable, RFA can obtain satisfying results.

Selected TACE

The 5-year survival among 173 patients treated with selected TACE and collected from two series, who had a single HCC less than 5 cm, and whose cirrhosis was not advanced, ranged from 33% to 53%, with a mean of 44%.25,26 As treatment was confined to one segment or to one subsegmental area, selected TACE presented no short-term complications or the problem of long-term liver function deterioration. In comparison, among 640 patients from different series with the same disease presentation and treated with the conventional whole-liver approach, 5-year survival ranged from 9% to 32%, with a mean of 13%.29

Discussion

The large number of patients enrolled in US screening programs has created a demand for effective, safe, repeatable, and economical treatment that can be made available in many centers. In the absence of randomized trials, it is and will be very difficult to find a consensual agreement on the indications for the respective therapeutic options. In our opinion, the only course at this time is to extrapolate from retrospective comparative studies and from studies on prognostic factors at least the unequivocal information that can prevent useless or even damaging therapies. Moreover, economic resources and the expertise available at each center are other factors that have a certain role in the choice of treatment.
Although it is understood that partial resection provides the highest possibility of completely ablating the tumor, in some studies the survival rates after surgery were roughly comparable with those obtained with PEI.4,35,41,42 A recent trial also obtained comparable results.43 In that study, 97 comparable patients with HCC less than 3 cm in diameter and three or less in number were treated during the same period, 39 with PEI and 58 with resection. Their 3- to 5-year survival was 59%–82% in the PEI group and 61%–84% in the surgery group. The explanation of this result probably reflects a balance among the advantages and disadvantages of the two therapies. Moreover, the results of surgery have been hampered by an incorrect selection of the patients, some of them being resected although having adverse prognostic factors. In fact, PEI survival curves are always better than curves for resected patients who present adverse prognostic factors. Another confirmation of such an interpretation comes from the report of the Liver Cancer Study Group of Japan. Three- and 5-year survival in Child’s class A patients with single HCC less than 5 cm was, respectively, 67% and 49% in the previous report of 1982–1989 (when PEI was not available) and 77% and 59% in the report of 1988–1995 (75% and 46% with PEI) because of better patient selection (perioperative mortality remained substantially unchanged) and the probable shift to PEI of some patients who, before the advent of PEI, would have been treated surgically.44

An open question remains the choice between PEI and RFA, or other ablation procedures. In our department we consider both the techniques, and also selected TACE, complementary, and use them according to the features of the disease, most notably, the size, number, and location of the tumor(s), presence of satellites, or portal thrombosis, and the response (Figs. 1, 2). This approach means a tailored strategy for every patient. A multifocal HCC can be treated with only one or with all the techniques, during a single hospital stay or over the years. For instance, in a patient with four lesions, three nodules can be treated with “single-session” RFA and the fourth with selected TACE if it is located in the upper part of segment 8 and not recognizable at US examination. Otherwise, the same lesion can also be treated with a combination of different techniques, when the first has had unsatisfactory results. Most lesions are currently treated with RFA. RFA obtained a higher rate of necrosis than PEI in small tumors (and in infiltrating lesions of any size) and avoided the side effects occurring after single-session PEI when a large amount (>60 ml) of ethanol was required.36 In multiple HCCs, RFA obtains greater local efficacy than whole-body (and lobar) TACE, without its side effects and without impairment of liver function.45 PEI is preferable in lesions at risk with RFA, such as those adjacent to main biliary ducts or intestinal loops (above all when fibrotic adhesions between the hepatic capsule and intestinal wall are suspected, because of the risk of perforation), in lesions difficult to approach or to treat because of the closeness of large vessels (sink effect), or protrusion from the capsule, and when a treatable portal thrombosis is present. Selected TACE is used in lesions not recognizable on US examination, in lesions not completely necrotized and presenting remnant vital tissue that is scattered or not recognizable on US examination for an additional treatment with RFA or PEI, and in the presence of satellite nodules after the achievement of complete necrosis of the main lesion. Our current results, obtained with the aforementioned combination of techniques, i.e., 82% and 68% at the 3- and 5-year follow-up in 116 Child’s A patients with single HCC less than 5 cm in diameter and normal bilirubin level, anticipate an increase in the survival previously achieved with only a single technique.

At the Consensus Conference of the EASL in Barcelona, PEI (and, indirectly, RFA) was validated as curative treatment only for HCC 3 cm or less in diameter, whereas the treatment of larger lesions (intermediate stage) needs validation with controlled randomized trials. Even though we agree with this statement, we prefer, at our center, while waiting for future results, to treat all patients with intermediate stage using a combination of percutaneous techniques, tailoring them according to the presentation of disease. Even though most patients present partial response and progressive disease over time, some of them are free of disease for years.

Conclusions

On the basis of the aforementioned studies, a tailored combination of RFA, PEI, and selected TACE is indicated as the treatment of choice for most patients enrolled by US screening, excluding those who are candidates for OLT and for partial resection. Unfortunately, OLT is available for very few patients, in western countries because of the shortage of donors, in poorer countries because of the lack of advanced technology, and in Japan because of ethical reasons. Candidates for partial resection should not present with the adverse prognostic factors detected during the past few years.6,46,47 In our opinion, resectable patients have to present with all the following factors:

a. Clinical. Child’s class A, transaminases less than 3 × normal values, age less than 70 years, no portal hypertension, serum bilirubin less than 1.5 mg/dl
b. Technical. Perioperative mortality risk less than 3%, (sub) segmentectomy feasible
Fig. 1. a Two nodules (arrows) of hepatocellular carcinoma (HCC) located in different segments of the right lobe, 3.0 cm and 2.7 cm in size, respectively, were treated with radiofrequency ablation (RFA). Spiral computed tomography (CT) scan during the arterial phase, obtained 8 months after treatment, shows complete absence of contrast enhancement within the tumors, which indicates apparent complete necrosis. b Spiral CT scan during arterial phase, obtained 12 months after treatment, shows the appearance of a new small hyperdense nodule, not detectable at ultrasound examination. c Arteriography confirms the hypervascularization of the new nodule. d Selected Lipiodol-transcatheter arterial chemoembolization (TACE) was performed, allowing nodule devascularization. e Plain CT scan obtained 4 months after TACE shows complete Lipiodol uptake of the nodule. f CT scan during arterial phase confirms complete necrosis of the nodules treated with RFA.
Fig. 2.  

a) CT scan during arterial phase shows single HCC, 5 cm in size, presenting an apparent complete necrosis after RFA performed 16 months before. At the baseline prior to therapy, alpha-fetoprotein (AFP) level was 560 ng/ml, and it was 65 ng/ml after therapy. 

b,c) At 24-month follow-up, CT scans show infiltrating local recurrence (arrows). AFP level was 1125 ng/ml.

d,e,f) A combination of treatments was used. In d, the CT scan shows the necrosis obtained with RFA; in e and f, arteriograms performed after RFA show the remnant part of vital tissue and its devascularization after selected TACE. At 32-month follow-up, the patient was apparently free of disease, and the AFP level was 54 ng/ml.
c. Neoplastic. No portal thrombosis, AFP less than 600ng/ml, single tumor (also with peripheral satellites, if anatomical resection is feasible)

However, it is still debatable whether a complex resection is an appropriate choice for a patient without adverse prognostic factors and a tumor less than 2 cm in diameter, when the possibility of peritumoral microinvasion is low and the rate of complete ablation with percutaneous ablation techniques is probably 100%. In practice, most patients could be managed as follows: early detection of the HCC by means of US screening in an at-risk population, treatment with percutaneous interventional techniques, follow-up with imaging methods and tumor markers (AFP, DCP), and further treatment of the new lesions.

References