15 Percutaneous Ethanol Injection

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CONTENTS

ABSTRACT

The chapter considers the principles, the techniques, the results of PEI for treating cirrhotic patients with HCC, and its current indications compared to those of RF, which is now considered the gold standard.

HCC is an organ pathology, so the first nodule detected is only a prelude to others. Therefore, hepatic resection or percutaneous ablation therapies can offer a palliative cure, achieving only a local control of the disease. Although it is understood that surgery assures the highest possibility to completely ablate the tumor and the possible satellites, recent RCTs comparing resection and percutaneous ablation therapies demonstrated roughly equivalent results.

As radiofrequency is actually considered the gold standard ablation technique, the current place of PEI has to be determined. Of course where radiofrequency is not available PEI remains a valid treatment for HCC, especially for health-care systems with limited economical resources. Moreover

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in all those cases in which radiofrequency is considered to be at risk for complications, PEI is a valid alternative, i.e., in case of lesions adjacent to main biliary ducts or to intestinal loops. PEI is also useful to treat lesions close to large vessels, as it is not affected by the so-called sink effect. PEI remains a good indication to treat segmental portal thrombosis.

Key Words: Percutaneous Ethanol Injection (PEI); Percutaneous Ablation Therapy (PAT); Radiofrequency (RF); Transarterial chemoembolization (TACE); Contrast-Enhanced Ultrasound (CEUS); Hepatocellular Carcinoma (HCC); Hepatic Resection (HR)

1. INTRODUCTION

Percutaneous ablation therapies (PATs) of hepatic neoplasms are performed using an image-guided approach through the liver parenchyma. PATs may be based on the use of means capable of destroying the tissue chemically, such as ethyl alcohol (PEI) or acetic acid (PAI), or physically, as with laser (ILP), radiofrequency (RF), or microwave (MW). PEI, the first of PATs to be proposed, was independently conceived at the University of Chiba in Japan and at the Vimercate Hospital (Milan) in Italy. The first study in an international journal appeared in 1986 *(1)*. On the basis of its rationale and the results obtained, the other techniques were subsequently designed *(2–5)*. The range of indications for PATs is currently wider compared to its initial use. Indeed, whereas for some years only patients with up to three small (max. 3 cm in size) or single (max. 5 cm in size) lesions were treated, with the introduction of the "single-session" procedure under general anesthesia *(6)*, even patients with lesions greater in number or larger in size could have been treated. This chapter considers the principles, the techniques, the results of PEI, and its current indications compared to those of RF, which is now considered the gold standard.

2. PRINCIPLES AND TECHNIQUES

PEI is generally performed under ultrasound (US) guidance, because real-time control allows faster execution, precise centering of the needle into the target, continuous monitoring of ethanol distribution, and determination of the appropriate amount of ethanol to be injected each time. The material to perform the procedure is very poor, consisting of a siring, a multihole 22 G needle, and a phial of 95% ethanol (Fig. 1). Alcohol acts by two mechanisms. The first is due to its diffusion within the cells, which causes immediate dehydration of cytoplasmic proteins with

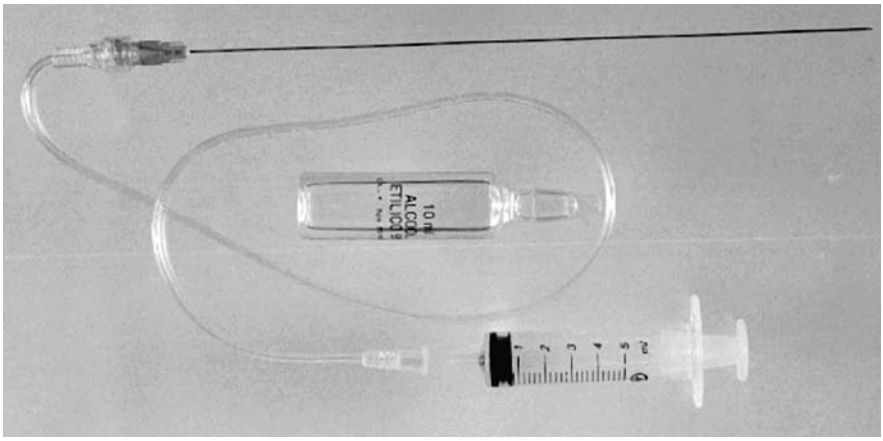

Fig. 1. Material used to perform PEI.

consequent coagulation necrosis followed by fibrosis. The second is due to its entrance in the circulation, which induces necrosis of endothelial cells and platelets 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 difference in consistence between neoplastic and cirrhotic tissue. Since 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. On the contrary, ethanol diffusion can be impaired in the presence of septa or even impossible in the presence of satellites because of the interposition of cirrhotic tissue *(7)*.

Conventional PEI is performed in multiple sessions on outpatient setting or, when the tumor is more advanced, in a "single session" under general anesthesia with the patient being hospitalized. The former technique is generally used for single HCC <4–5 cm in diameter or for multiple HCC with 2–3 nodules ≤3 cm in diameter. The number of sessions is approximately twice the diameter of the lesion in centimeters *(8)*. The latter technique is adopted for more advanced HCC, single or multiple, that does not involve more than 30% of the hepatic volume and with no neoplastic thrombosis in the main portal branches or in the hepatic veins *(9)*. PEI can also be performed in selected patients with segmental or subsegmental portal thrombosis, injecting 1–3 ml of ethanol directly into the thrombus *(10)*. More detailed technical information about the procedures are available in several studies *(7–12)*.

Recently the use of a multipronged needle to treat medium to large HCC has been proposed. However, there is concern about its safety as

inserting this kind of needle is more technically demanding compared to the conventional one and placing any of its tines outside the tumor can cause alcohol spill, increasing the risk of complications *(13)*.

3. 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

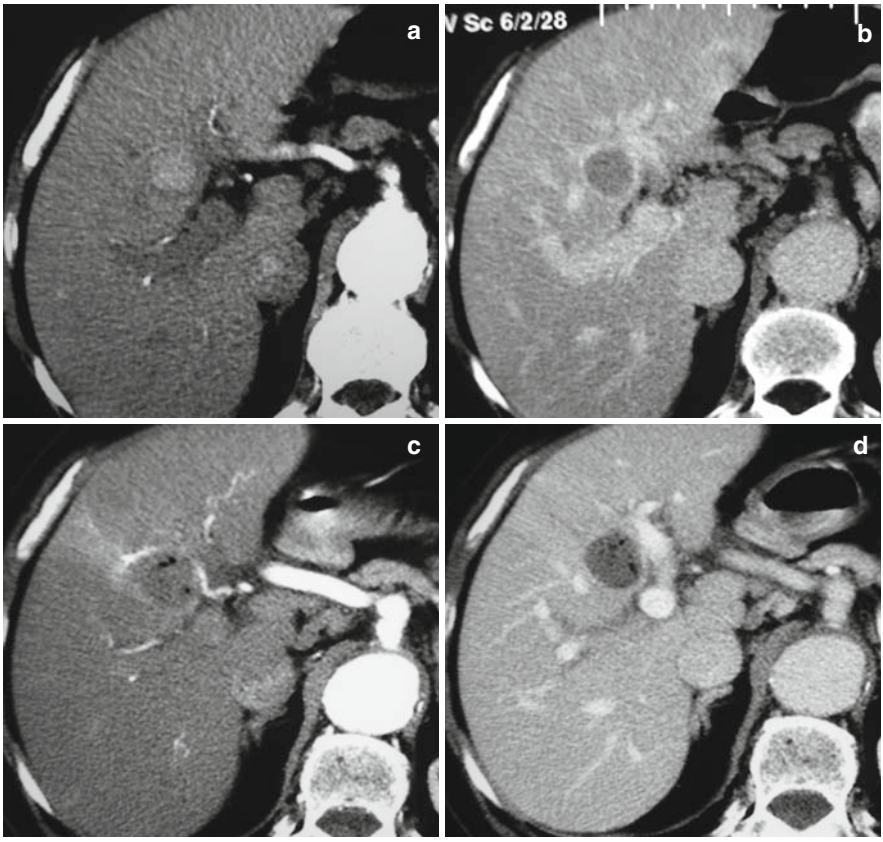

Fig. 2. Transverse CT scans showing a HCC of 2 cm in the right lobe treated with multisession PEI. (**a**, **b**) Before treatment the tumor shows hypervascularity during the arterial phase and washout in the portal phase. (**c**, **d**) The arterial and portal phase CT scans the day after treatment show a completely necrotic lesion because of the absence of enhancement. Very small bubbles of gas due to recent necrosis are detectable inside the treated area.

markers is used. They are the same as those adopted during initial staging and controls. Since there are many investigations and some of them are comparable, we prefer to routinely use only contrast-enhanced US (CEUS) (with SonoVue, Bracco, Milan, Italy) and spiral multislice CT (Fig. 2) with the triphasic technique (4–5 ml/s, 30, 70, and 120 s after the injection of contrast medium). Other imaging techniques (angiography, MR, PET) or biopsy is performed only in rare cases, if there is a doubt whether the response is partial or complete. If the areas of viable tissue are very small, beyond the

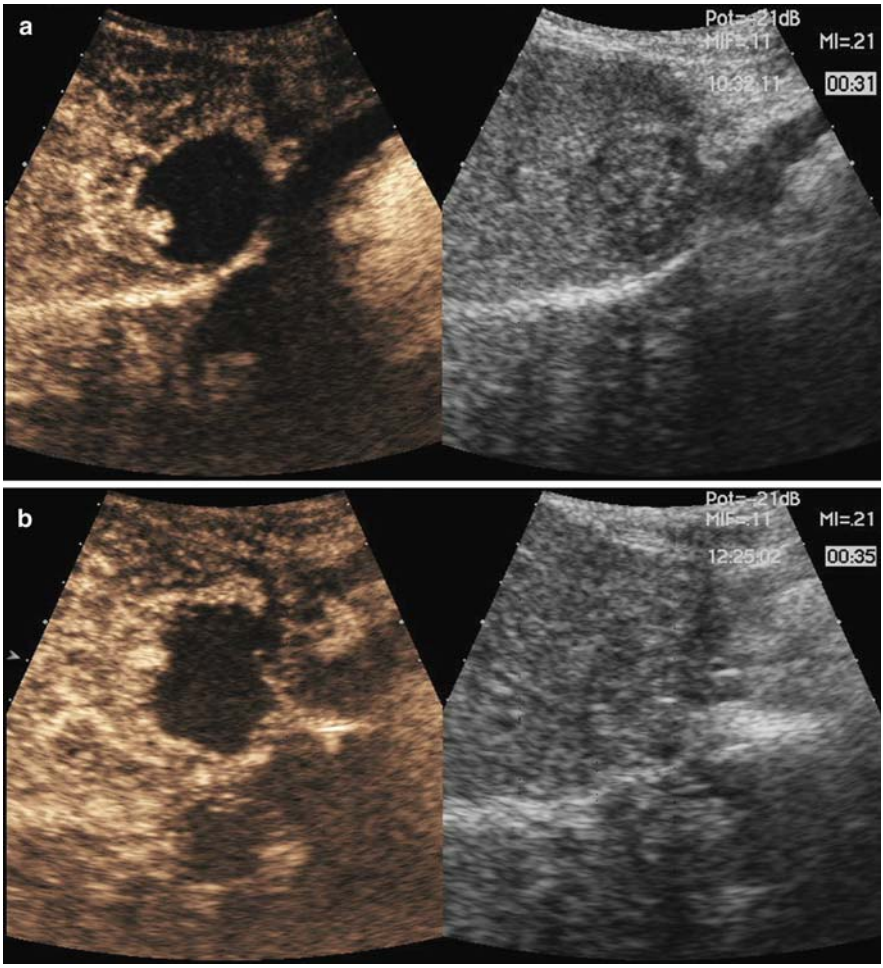

Fig. 3. Contrast-enhanced US scans showing a HCC nodule treated with multisession PEI. (**a**) Vital hypervascularized tissue remains present after the first session. (**b**) After the second treatment, targeted using contrast-enhanced US as guidance, the lesion is completely treated.

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 follow-up if they are evidenced as zones of enhancement at CT or CEUS. The response is considered complete when CT and CEUS scans show the total disappearance of enhancement within the neoplastic tissue and when the same picture is confirmed at scans performed at successive controls.

The absence of enhancement means the absence of blood flow due to necrotic and fibrotic modifications. Even with such characteristics, the necrotic area does not disappear and remains visible in place of the tumor even if reduced in size to different extents.

CEUS is particularly useful *(14–15)* during multisession treatment as it permits to evaluate before each session if there is persistence of any viable area. The following instillation of ethanol can therefore be selectively performed in the tumoral tissue (Fig. 3).

As tumor markers, we use α-fetoprotein (AFP) and des-γ-carboxy-prothrombin (DCP), which are often complementary. Nevertheless, their assay is useful only if they were abnormal before treatment. When the imaging techniques show a complete response not followed by normalization of 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 control with CEUS and/or CT is carried out according to the procedure used. If the multisession procedure is performed, the control is made when the treatment is presumed to be complete. If the "single-session" procedure is performed, the control is made the day after treatment. After that these imaging examinations and serum assay of tumor markers are performed every 4–6 months.

4. COMPLICATIONS

Mortality related to conventional treatment is negligible, because only few anecdotal cases were reported in thousands of patients treated. In a review study with 1066 patients treated in 8118 sessions, one death (0.09%) occurred *(16)*. Major complications are rare, ranging from 1.3 to 2.4%, and usually treated conservatively (intraperitoneal hemorrhage, cholangitis, jaundice secondary to injury of main bile ducts, liver abscess, hemobilia, arterioportal shunt, shock, and segmental hepatic infarction).

With the "single-session" technique, where larger volumes of ethanol are administered, the mortality (0.9%) and the complication rate increase (4.5%), and other major complications can occur (transient worsening of portal hypertension with risk of hemorrhage from esophageal varices, liver decompensation, transient alcohol intoxication) *(9)*.

A particular and late type of complication is seeding, which may occur despite the use of small needles and injecting alcohol down the track. In a recent study *(17)* with a large cohort of patients, the authors registered five cases of seeding out of 270 patients (1.8%).

A review article *(18)* evaluated all the cases of seeding following PEI without prior biopsy reported between January 1983 and February 2007. A total of 16 papers describing 26 cases of seeding were found. The most common site of seeding was intraperitoneal and the median time from PEI to detecting seeding was 6 months.

5. RESULTS

5.1. Survival Studies

Numerous long-term survival curves have been published. The more important studies in terms of quality and quantity were conducted in Italy and in Japan [7-8-11-12]. Their 5-year survival, in patients with single HCC $\leq$5 cm or with $\leq$3 nodules $\leq$3 cm, ranged from 43 to 63%. Most recently Ebara *(17)* reported an overall 3- and 5-year survival rates of 81.6% and 60.3%, respectively. The rates were higher (87.3% at 3 years and 78.3% at 5 years) in Child A patients with a solitary tumor $\leq$2 cm in diameter.

Main pretreatment factors influencing survival are liver function, tumoral markers (AFP, DCP) level, number, and size of tumors. A post-treatment prognostic factor is the complete response to PAT *(19)*. The main cause of death in Child A patients was progression of neoplastic disease due mainly to the appearance of new lesions, while in Child C patients the cause of death was hepatic insufficiency, questioning the useless of treatment in these patients.

The incidence of appearance of new lesions at 5 years ranged from 64 to 87%, i.e., the same rates showed after surgery. The incidence of local recurrences ranged from 4 to 17%, usually due to the tumor.

Following these results, the European and the American Associations for the Study of the Liver included PEI among the treatments considered effective for early-stage disease *(20)*.

5.2. Comparison to Other Therapies

In all the randomized controlled trials (RCTs), RF showed better local efficacy and required fewer treatment sessions compared to PEI, but PEI presented a minor rate of adverse events *(21, 22)*. In particular, in tumor <3 cm in size, RF obtained a complete ablation in nearly the totality of cases, while PEI obtained approximately 10% less. Successively, RF was compared to PEI for long-term results. In all the RCTs, RF was superior

to PEI with respect to local recurrence, overall survival, and cancer-free survival *(23–25)*. For explaining the difference regarding these parameters, it is important to remember that also at the earliest stages *(26)* different degrees of tissue differentiation are possible. Histopathologic studies have revealed that, while nodules measuring 1.5 cm or less (considered the early stage for pathologists) are uniformly well differentiated, those between 1.5 and 2.0 cm in diameter often contain zones of less-differentiated tissue with more intense proliferative activity (considered the small advanced stage for pathologists) *(27–29)*. The less-differentiated areas give rise to portal microinvasion in 10% of the cases and to microsatellites in 3% of the cases, usually within 1.0 cm of the main tumor *(28–31)*. Better long-term results of RF are due to the fact that thermoablation in most cases of early stages is able to obtain a 0.5–1.0 cm safety margin around the tumor, reducing the appearance of possible microsatellites during the follow-up. RF resulted superior to PEI also in tumors of medium and large size *(32)*.

Recently an RCT on 184 patients with HCC $\leq$3 cm found that RF was superior to PEI and PAI with respect to local recurrence, overall survival, and cancer-free survival rates, even if RF caused more major complications (4.8% vs 0%). No statistically significant difference was reported between PEI and PAI *(33)*.

Some retrospective studies comparing PEI and hepatic resection (HR) showed 5-year survival rates broadly equivalent, with an approximate rate of 50% for both *(34–37)*. These data were recently confirmed by the only RCT which compared patients with one or two nodules $\leq$3 cm in size, which did not find any statistical difference for recurrence rate and survival *(38)*.

5.3. Combined Therapies

Combined therapy with PEI and RF for large HCC has been proposed demonstrating that the two techniques cause a synergistic necrotizing effect, with coagulation volumes larger than those usually obtained with PEI or RFA alone *(39*, *40)*. Recently the combination of repeated single-session PEI and transarterial chemoembolization (TACE) has been compared to repeated single-session PEI in patients with nonresectable HCC *(41)*. The combination of TACE and PEI was associated with a longer survival (1-, 3-, and 5-year survival: 90, 52, and 43%, respectively) compared to PEI treatment alone (1-, 3-, and 5-year survival: 65, 50, and 37%, respectively).

6. CONCLUSIONS AND CURRENT INDICATIONS

HCC usually coexists with an underlying hepatic chronic disease. According to the stage, one disease will prevail over the other. For such reason, therapies should not worsen liver function. HCC is an organ

pathology, so the first nodule detected is only a prelude to others. A study on resected patients demonstrated that multicentricity is already present in 50% of early stages and that 93% of patients with single minute HCC presented other nodules within 5 years *(42)*. Being multicentric over time, HCC needs multistep treatments.

Therefore HR (or PATs) can offer a palliative cure, achieving only a local control of the disease. In fact, according to a Japanese nationwide survey, only 1.6% of all resected patients presenting intrahepatic recurrence were re-resected *(43)*.

Although it is understood that HR assures the highest possibility to completely ablate the tumor and the possible satellites, different comparative studies based on historical results *(35–37)* and the recent RCTs comparing HR and PATs demonstrated roughly equivalent results *(34*, *38*, *44*, *45)*. The explanation is probably due to a balance between advantages and disadvantages of the two therapies, the most important advantages of PATs being repeatability, no loss or damage of non-neoplastic tissue, and lower complication rates. Moreover, the overall results of both therapies were hampered and flattened by an incorrect selection of the patients, part of them being treated even though they had adverse prognostic factors for that specific treatment. For instance, the Liver Unit of Barcelona reported the usual, i.e., the mean rate reported by most studies, 5-year overall survival rate of around 50% after HR *(46)*. However, when the patients were divided according to two simple adverse prognostic factors, i.e., portal hypertension and abnormal bilirubin, a rate of 74% was obtained (the best so far reported) in patients with normal values and a rate of only 25% in the worst candidates. The fact that the survival of this second group of patients was comparable with recently reported survival rates from two series of untreated patients (20 and 16%, respectively), even though with a more adverse profile *(47*, *48)*, questions the indication for surgery in such patients that are probably more eligible for PATs.

These considerations suggest that the best strategy has to be tailored according to the individual presentation of the disease. In single operable nodule <3 cm, there is no clear evidence to establish the best treatment. Accordingly, each referral center follows a personal algorithm for such borderline patients. Currently, RF is becoming the gold standard for nodules <2 cm *(49)*, while for nodules between 2 and 3 cm the choice is reached according to individual factors.

As RF is actually considered the gold standard ablation technique, the current place of PEI has to be determined. Of course where RF is not available PEI remains a valid treatment for HCC, especially for health-care systems with limited economical resources as studies related to the total cost of treatment reported an average of only 700–1000 $ for PEI *(8*, *50)*.

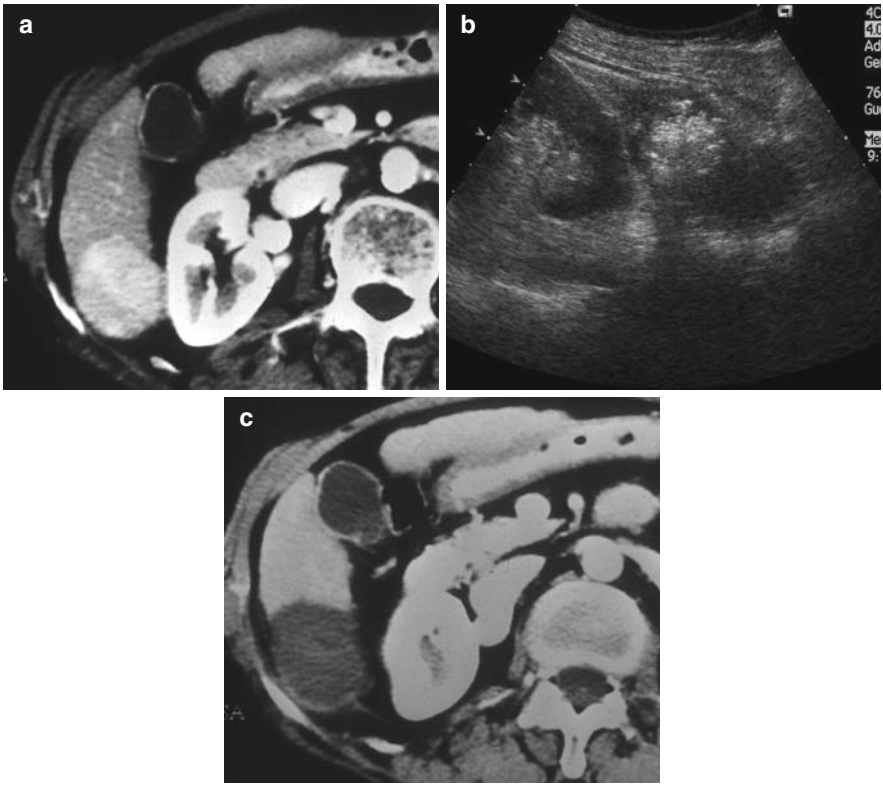

Fig. 4. Transverse CT and US scans showing a HCC of 4.2 cm located in segment VI, close to the bowel, treated with single-session PEI because of its at-risk location. (**a**) At the baseline the lesion appears well vascularized at arterial phase CT scan. (**b**) US scan at the end of the procedure shows the hyperechoic zone of ethanol filling the tumor. (**c**) At the arterial phase CT scan 1 month after treatment no enhancement is visible within the tumor.

Moreover in all those cases in which RF is considered to be at risk for complications, PEI is a valid alternative, i.e., in case of lesions adjacent to main biliary ducts (because of the risk of stenosis) or to intestinal loops (Fig. 4) (above all when fibrotic adhesions between the hepatic capsule and the intestinal wall are suspected, because of the risk of perforation) *(51)*. Combined therapies have been also proposed for these kinds of lesions *(52*, *53)*. PEI is also useful to treat lesions close to large vessels, as it is not affected by the so-called sink effect. PEI remains a good indication to treat segmental portal thrombosis.

In our department we consider PEI and RF, and also selective TACE, complementary, and use them according to the presentation of the disease, i.e., size, number, location, and presence of satellites or portal thrombosis. A

multifocal HCC can be treated with only one or with all the techniques, during a single hospital stay or over the years. Our longest survivor, currently free of disease, was initially treated 19 years ago with PEI and when new lesions appeared during follow-up, he was treated with RF, selective TACE, and again PEI. Otherwise, the same lesion can also be treated with the combination of different techniques when the first has resulted unsatisfactory.

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