Cardiovasc Intervent Radiol (1997) 20:204–210

CardioVascular and Interventional Radiology

Pictorial Essays

Ablation of Hepatocellular Carcinoma by Percutaneous Ethanol Injection: Imaging Findings

Christoph D. Becker,[1] Marianne Grossholz,[1] Gilles Mentha,[2] Arnaud Roth,[2] Emiliano Giostra,[3] Pierre-Alain Schneider,[1] François Terrier[1]

[1] Division of Diagnostic and Interventional Radiology, University Hospital of Geneva, 24 Rue Micheli-du-Crest, CH–1211 Geneva, Switzerland

[2] Department of Surgery, University of Geneva, 24 Rue Micheli-du-Crest, CH–1211 Geneva, Switzerland

[3] Division of Gastroenterology, University Hospital of Geneva, 24 Rue Micheli-du-Crest, CH–1211 Geneva, Switzerland

Percutaneous ethanol injection (PEI) is an accepted treatment option for selected patients with hepatocellular carcinoma (HCC). PEI induces local tumor necrosis as a result of protein denaturation, cellular dehydration, and occlusion of small vessels. PEI allows selective treatment of limited HCC without significant side effects on the adjacent liver parenchyma, and is, therefore, suitable even in advanced stages of cirrhosis with impaired liver function [1–3]. PEI has also been used to treat secondary hepatic neoplasms under certain circumstances, but its role and efficacy for this purpose remain to be defined [4].

Another well-established modality for treating unresectable HCC is intraarterial chemoembolization. This is often performed with an emulsion of doxorubicin and lipiodol which accumulates preferentially within HCC nodules. The intraarterial technique can be used as a regional or segmental treatment and is particularly suitable in the presence of daughter nodules or multiple HCC. To combine the advantages of intravascular segmental treatment and direct percutaneous local treatment of tumor nodules it has been recommended to use chemoembolization and PEI sequentially [5]. Our current treatment protocol for unresectable HCC is as follows. Single nodules with a diameter <3 cm are treated with PEI alone. Single nodules <5 cm and up to three lesions <3 cm are treated with a combination of chemoembolization and PEI. Patients with nodules >5 cm or with widespread tumor disease are not treated with PEI but with chemoembolization alone or with systemic chemotherapy, or are given no treatment at all.

The technique of PEI has been well described [1–3]. The total volume of ethanol to be injected into a neoplastic lesion may be determined according to the formula $V = {}^4/_3\pi\ (0.5 + r)^3$, where V is the volume in milliliters, and r the radius of the lesion in centimeters. Treatment protocols vary in terms of volume of absolute ethanol administered per session, and in using PEI either alone or combined with intraarterial chemoembolization [2, 5, 6]. Although the response to PEI is most promising in lesions <3 cm, ablation of larger tumors is also feasible.

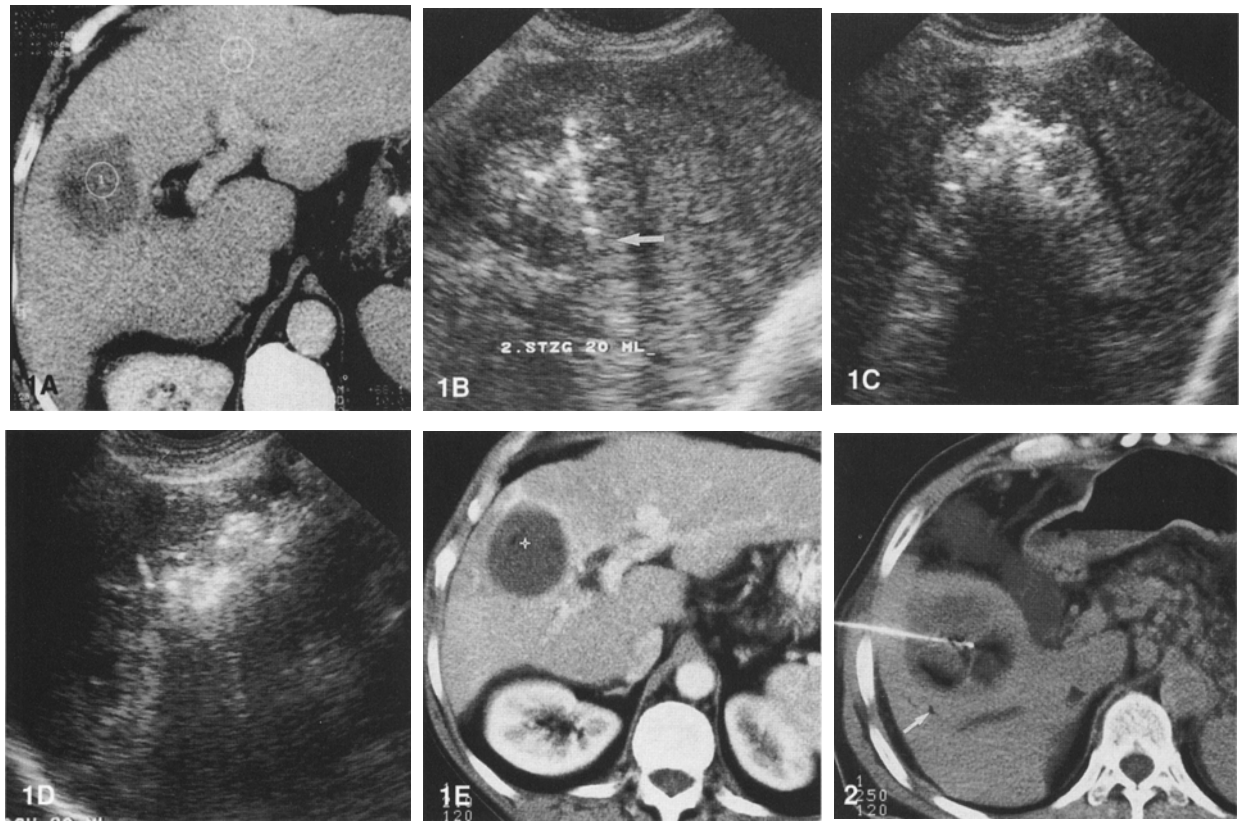
Needle placement, monitoring of PEI, assessment of the treatment effect, and follow-up are done with cross-sectional imaging techniques. Image-guided fine-needle aspiration biopsy enables direct cytologic proof of residual or recurrent tumor, but negative sampling errors may easily occur in treated, partially necrotic lesions. Therefore, knowledge of the changes observed on cross-sectional images obtained during and after PEI greatly facilitates diagnostic and therapeutic decisions.

We have used PEI with ultrasound (US) and computed tomography (CT) guidance, either alone or in combination with chemoembolization, in 35 patients; 32 of these had histologically proven HCC and 3 had secondary lesions of gastrointestinal neoplasms. We describe the immediate, early, and late changes observed on US, CT, and magnetic resonance (MR) images after PEI treatment.

Monitoring of PEI

PEI may be done with US guidance whenever the lesion to be treated is sufficiently well visualized. In addition to its low cost and availability, US monitoring offers the advantage of visualizing the distribution of ethanol directly because microbubbles injected with the ethanol are hyperechogenic (Fig. 1). However, when

Correspondence to: C.D. Becker, M.D.



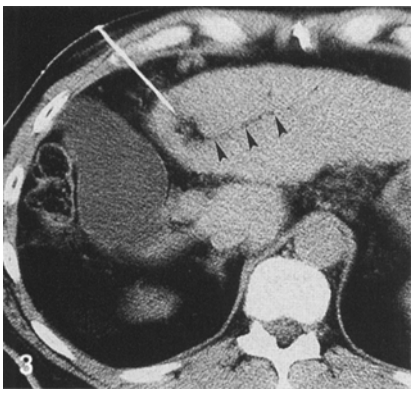


Fig. 1. US-guided percutaneous ethanol injection (PEI) of hepatocellular carcinoma (HCC) and follow-up with CT. **A** Contrast enhanced CT scan (venous phase) shows a hypoattenuating mass 5 cm in diameter within the right hepatic lobe corresponding to a single HCC nodule. **B** On US, the mass is hyperechogenic and well defined. A special 21 gauge needle with multiple side holes but no end hole (Ago Pia, Milan, Italy), has been inserted under US guidance; the position of the needle tip close to the posterior border of the lesion (arrow) indicates that the side holes are in an appropriate position. **C** Injection of ethanol causes echogenic artifacts within the lesion and acoustic shadowing due to microbubbles, thus allowing real-time monitoring of the distribution of ethanol. **D** After injection of 20 ml of ethanol, the lesion becomes obscured by these artifacts. **E** Contrast enhanced spiral CT (venous phase) obtained 24 hr later demonstrates the effect of PEI. The smooth, regular, enhancing rim around the nonenhancing tumor persisting in the venous phase was interpreted as reactive hyperemia rather than residual tumor. No further treatment was given. There was no evidence of residual tumor or local tumor recurrence on follow-up.

Fig. 2. CT-guided PEI of large HCC. HCC lesion 5 cm in diameter was treated with a total volume of 170 ml of absolute ethanol administered in six PEI sessions. The distribution of ethanol is well visualized because it is hypoattenuating compared with tumor and liver tissue. Note that some ethanol is visible in the liver tissue adjacent to the tumor (arrow).

Fig. 3. Periportal tracking of ethanol during CT-guided PEI of a recurrent HCC nodule in the left hepatic lobe after right hepatectomy. Hypoattenuating ethanol is not only seen within the treated lesion but also follows a linear track along the portal system of the left hepatic lobe (arrowheads).

large volumes of ethanol are injected, the lesion eventually becomes obscured by acoustic shadowing and reverberation artifacts (Fig. 1D). CT guidance is preferred for PEI whenever US does not permit sufficient visualization of the lesion to enable the needle to be placed correctly, particularly in large tumors that often require multiple PEI sessions (Fig. 2). Contrast-enhanced dynamic CT and, especially, spiral CT is superior to US for visualizing the extent of necrosis induced by PEI. PEI-induced necrosis results in a lack of enhancement, and the hypodense, necrotic areas are well delineated on CT, usually with attenuation values of 30–35 HU (Fig. 1E). Injected ethanol may be visualized on CT as it is hypoattenuating compared with tumor and liver tissue and even more hypoattenuating than necrosis (<200 HU) (Fig. 2). Extratumoral tracking of ethanol is seen after injection of large volumes and usually occurs along the portal triad (Fig. 3). If PEI

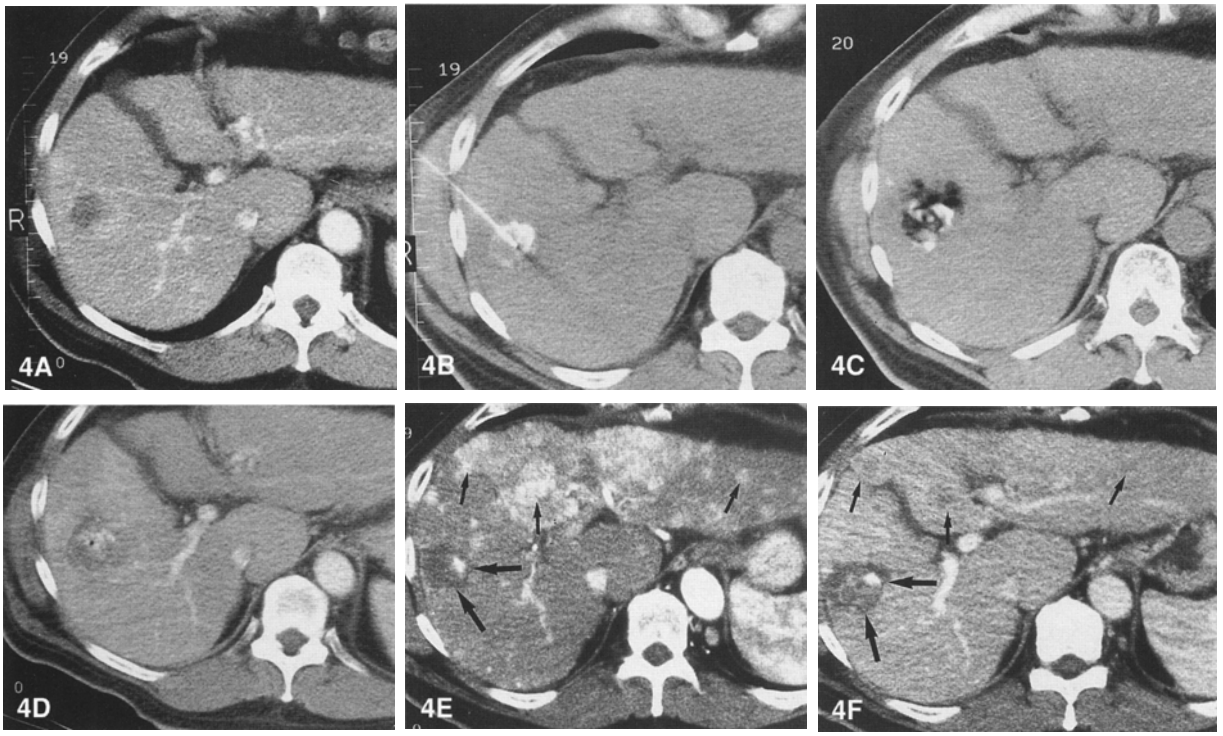


Fig. 4. Combined treatment of HCC with chemoembolization and PEI: immediate CT findings. **A** Contrast-enhanced spiral CT shows a HCC with a diameter of 3 cm before treatment with chemoembolization with doxorubicin and iodized oil. **B** Unenhanced scan obtained 4 weeks after selective intraarterial chemoembolization and immediately before PEI. The lesion is hyperattenuating due to retention of iodized oil. **C** Unenhanced scan obtained immediately after PEI. A mixed-density pattern is seen owing to the hypoattenuating ethanol. **D** Early follow-up. Contrast-enhanced spiral CT scan obtained for follow-up several days after PEI. The hypoattenuating areas have disappeared, but some residual hyperattenuating areas due to iodized oil are still visible. **E, F** Follow-up study obtained 10 months after treatment because of rising alpha-fetoprotein levels. Dual-phase spiral CT, same study. **E** Arterial phase. The treated lesion within the right lobe shows no enhancement (large arrows). Some residual hyperattenuating lipiodol is visible within the lesion. However, there are now multiple hyperattenuating lesions visible mainly throughout the left hepatic lobe (small arrows). **F** Venous phase. The treated lesion shows no enhancement (large arrows). The small nodules are less well visualized than in the arterial phase because they have become almost isoattenuating or slightly hypoattenuating with the surrounding liver parenchyma (small arrows).

is done after chemoembolization, a mixed-density pattern may be observed due to hyperattenuating, retained, iodized oil and hypoattenuating ethanol (Fig. 4). Tumors that are well defined, such as HCC with a capsule, are well suited for PEI because the ethanol distributes relatively homogeneously within the lesion (Figs. 1, 2, 4, 5). PEI of poorly defined, infiltrating tumors is more difficult to control (Fig. 6).

Early Follow-up After PEI

Follow-up studies at defined intervals are necessary in order to evaluate the effect of PEI and to detect residual, recurrent, or new tumor manifestations. Routine controls should include biochemical tumor markers, such as alpha-fetoprotein levels, and image-guided biopsies. However, tumor markers may fail to be elevated before PEI, and cytologic examination may be false negative after PEI in a considerable number of cases. Therefore, the findings on diagnostic imaging studies must also be taken into consideration.

Contrast-enhanced, dynamic, incremental or spiral CT is currently the most common imaging technique for follow-up after PEI. The typical behavior of HCC nodules on CT is hyperattenuation compared with the surrounding liver parenchyma in the arterial phase, often followed by hypoattenuation in the venous phase. Therefore, CT is best performed in the form of dual-phase spiral CT with an arterial and venous phase (Fig. 4E, F). CT studies of large tumors obtained within 24–48 hr after PEI may show small gas collections. Although these are often due to small injected air bubbles, gas formation may also occur due to tissue necrosis [6]. As with arterial embolization, these changes usually disappear spontaneously and should not be mistaken for abscess formation. Several investigators have shown that circumscribed, nodular enhancement in the area of the treated lesion is a reliable indicator of residual tumor [6–8] (Figs. 5B, 6B). Occasionally, smooth, regular, peripheral enhancement may be seen corresponding to reactive hyperemia (Fig. 1E). Ebara et al. [8] have shown that residual tumor shows enhancement in the early but not in the late phase,

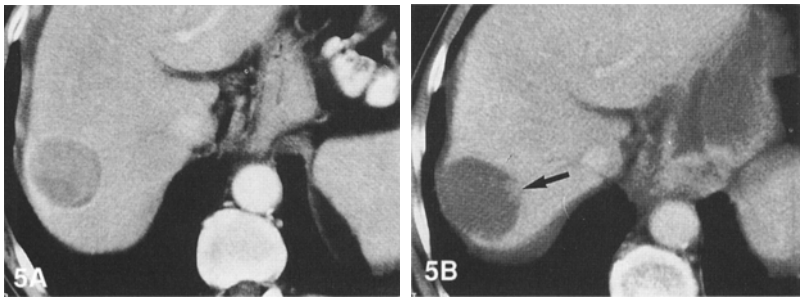


Fig. 5. Encapsulated HCC treated with PEI alone: early follow-up with CT. **A** Contrast-enhanced spiral CT shows a HCC lesion with an enhancing capsule before treatment with 40 ml of ethanol under US guidance in one session. **B** On the contrast-enhanced spiral CT image the treated lesion remains unenhanced, but a small nodular area of enhancement is seen close to the capsule, corresponding to viable tumor (arrow).

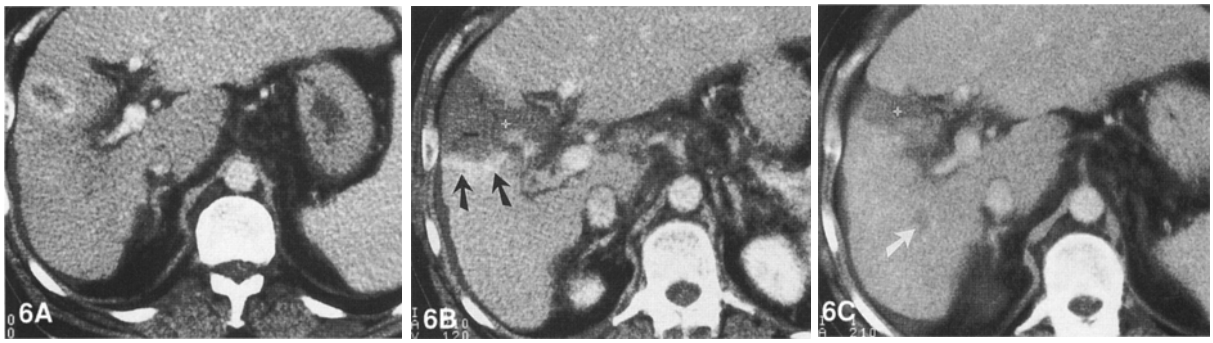


Fig. 6. Infiltrating HCC treated with PEI alone: findings on contrast-enhanced spiral CT. **A** A hypervascular HCC is seen in the left lobe (segment 4) of a cirrhotic liver. The lesion is poorly defined against the surrounding parenchyma. **B** One day after PEI, a large hypoattenuating area is seen in segment 4, indicating necrosis. The enhancing area (arrows) corresponded to residual viable tumor on fine-needle aspiration biopsy and additional treatment was needed. **C** Six months later, the area of necrosis has decreased in size, indicating local tumor control. However, a small secondary lesion has appeared in the right lobe (arrow).

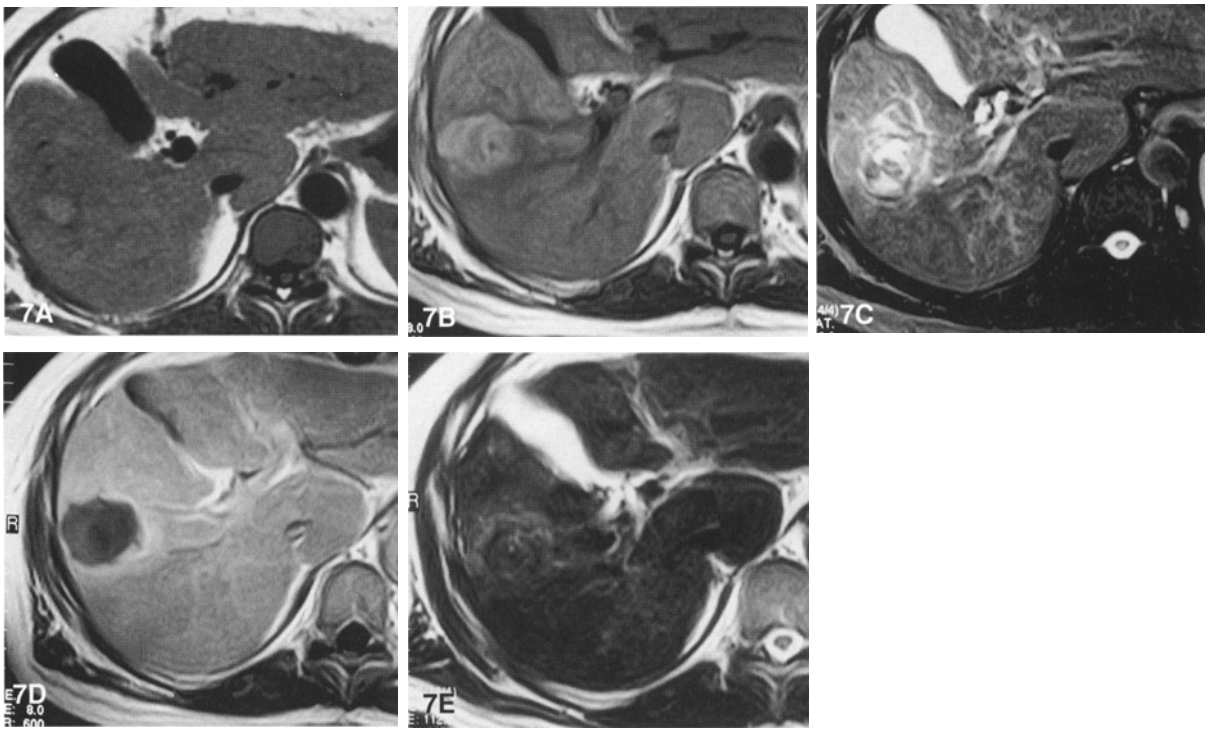


Fig. 7. Small HCC treated with PEI and chemoembolization: MR findings. **A** Before treatment. On the unenhanced T1-weighted SE image a hyperintense nodule of 2 cm is seen in the right hepatic lobe, which corresponded to an HCC nodule. **B** Early findings after PEI. On the unenhanced T1-weighted SE image obtained after chemoembolization with doxorubicin and iodized oil and PEI, the hyperintense area has become much larger, probably due to hemorrhage. **C** On the corresponding T2-weighted FSE image (with fat saturation), the lesion is hyperintense. This could be due to hemorrhage or liquefactive necrosis or residual viable tumor. **D** On the gadolinium-DTPA-enhanced T1-weighted SE image the center of the lesion lacks enhancement, but there is intense enhancement at the periphery. These findings indicate that the center of the lesion has become necrotic but that residual viable tumor may be present at the periphery. **E** Follow-up 3 months after additional PEI. T2-weighted FSE image at the same level as **C** shows a lack of signal within the tumor. The lesion is almost isointense compared with the surrounding parenchyma. These findings indicate coagulative necrosis.

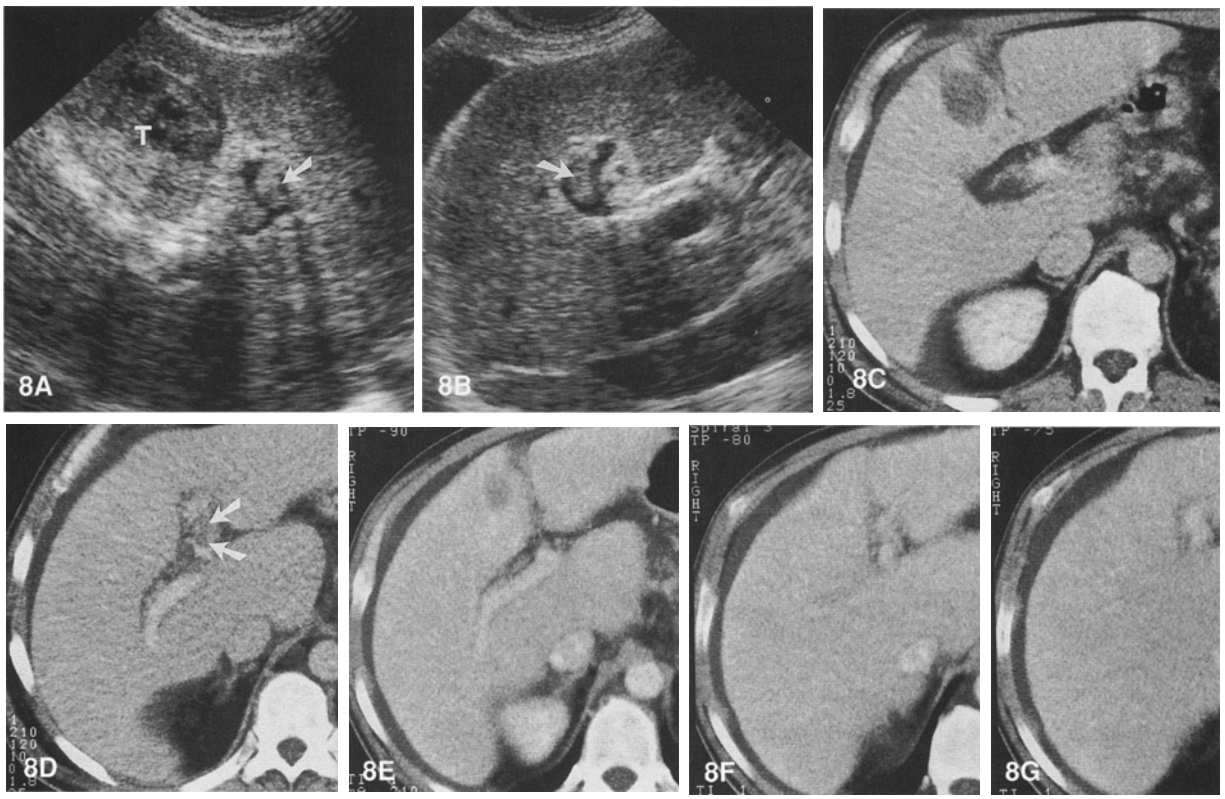


Fig. 8. Chemical portal vein thrombus following US-guided PEI. Patency of the portal vein had been documented before US-guided PEI in this patient with a HCC in segment 4, adjacent to the left portal vein. The axial US image **A** and the sagittal image **B** were obtained 24 hr after PEI and show the tumor (*T*), and a solid thrombus in the left portal branch adjacent to the tumor (arrows). **C, D** These contrast-enhanced spiral CT images were obtained 6 days after US-guided PEI, and confirm the presence of a solid floating thrombus in the left main portal branch (arrows). **E–G** Contrast-enhanced spiral CT was repeated 4 months later. At this time, the tumor has decreased in size **E**, and the thrombus has disappeared (**F, G**).

whereas reactive inflammation shows enhancement in both the early and the late phase.

Investigation of the MR imaging findings after PEI has mainly been focused on HCC [9–15]. Although the spatial resolution of MR images is currently still inferior to that of CT images and T2-weighted images often suffer from motion artifacts, it has been shown that MR may be used as an alternative to CT to evaluate the effect of PEI. The signal changes observed on MR images after PEI are somewhat more complex than the changes observed on CT scans. The MR imaging appearance of untreated HCC is variable. This may be attributable to several factors, including magnetic field strength, tumor size, histologic tumor grade, presence of a capsule, and fatty or hemorrhagic intratumoral changes. On unenhanced T1-weighted images, HCC may be hyperintense (Fig. 7A), hypointense, or isointense relative to surrounding liver tissue. There is no uniform behavior after intravenous injection of gadolinium chelates, although most lesions show at least some enhancement [9–11]. On unenhanced, T2-weighted images, over 80% of HCC are moderately to strongly hyperintense, but a significant minority is iso- or hypointense [9, 12, 13]. The MR signal changes of HCC induced by PEI with and without concomitant chemoembolization have been analyzed in several studies. The signal patterns on unenhanced T1-weighted images are variable and nonspecific [9, 14]. An increased signal intensity within or around the lesion may be observed in the early phase after PEI and can be explained by hemorrhage (Fig. 7B). High-signal areas on T2-weighted images may correspond with hemorrhage or liquefactive necrosis or reactive inflammation but also with residual viable tumor (Fig. 7C) [11, 15]. However, a homogeneously hypointense signal of a previously hyperintense tumor on a T2-weighted sequence seems to correlate with coagulative necrosis (Fig. 7E). In cases of doubt, T1-weighted images obtained after intravenous administration of gadolinium chelates may be used to distinguish viable tumor from liquefactive necrosis, since tumor shows enhancement and necrosis does not [15] (Fig. 7D). Although the necrotizing effects of PEI and of chemoembolization with iodized oil are different, the effects observed on MR images after the combination of these two modalities are the same as with PEI alone. Bartolozzi et al. [14] have shown that retention of iodized oil after chemoembolization does not interfere with the

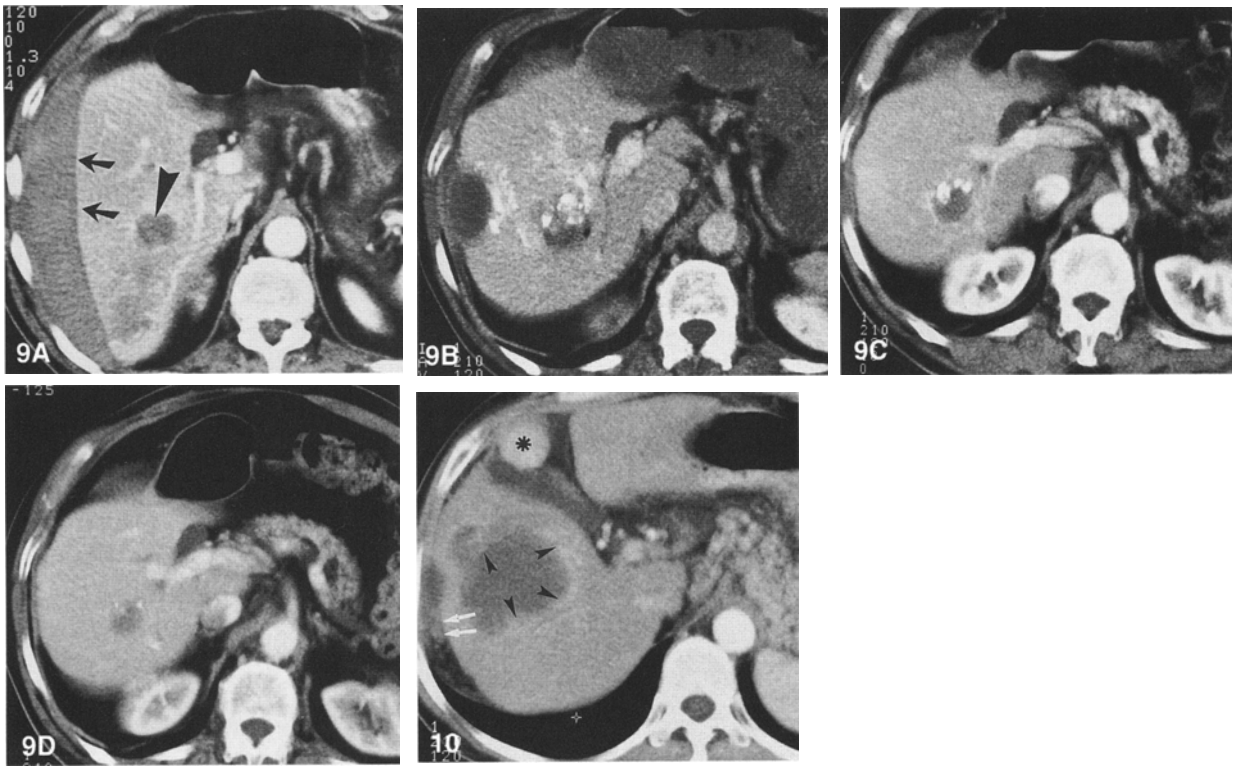


Fig. 9. Long-term follow-up after PEI of a small HCC in a noncirrhotic liver. **A** Contrast-enhanced spiral CT image shows a 3-cm HCC in the right lobe of a noncirrhotic liver (arrowhead). The tumor became manifest due to massive subcapsular hemorrhage (arrows) and a biopsy was done after spontaneous resolution of the hematoma. The serum alpha-fetoprotein level was significantly elevated. **B** Contrast-enhanced spiral CT image obtained immediately after PEI. Some densely hyperattenuating areas within the lesion are due to previous angiography with injection of iodized oil. Note the residual subcapsular hematoma. After three sessions of PEI, the alpha-fetoprotein levels became normal and remained so during further follow-up. **C, D** Contrast-enhanced spiral CT images show the lesion 7 months and 2.5 years after PEI; there was no evidence of tumor growth.

Fig. 10. Needle-tract seeding after PEI of HCC. Contrast-enhanced spiral CT image obtained 8 months after six PEI treatment sessions of the large HCC shown in Figure 2. At the previous puncture sites there is diffuse perihepatic infiltration corresponding with needle-tract seeding (arrows). Intrahepatically, there are multiple areas of nodular enhancement at the periphery of the treated lesion, consistent with recurrent tumor growth (arrowheads). However, biopsy of the second enhancing nodule adjacent to the gallbladder (asterisk) revealed no malignant cells.

MR signal pattern. This may in fact be an advantage of MR imaging compared with CT, on which retained iodized oil alters the attenuation values considerably (Figs. 4, 9). It is likely that the recent technical advances in the field of MRI, such as fast and "ultrafast" sequences, will improve the quality of T2-weighted images as motion artifacts due to respiration can be reduced.

Gray-scale US cannot reliably delineate residual viable tumor tissue. Color Doppler US has been recommended for assessing the effect of PEI treatment [16]. In our experience, however, only a minority of HCC showed an adequate color flow signal due to hypervascularity that would have enabled us to detect small residual foci of viable tumor. Power Doppler may enhance the ability of US to detect small tumor foci with moderate vascularity. The role of [^{18}F]fluorodeoxyglucose positron-emission tomographic imaging remains to be determined [17]. Selective arteriography has been used in early studies [1] but appears too invasive for serial follow-up tests after PEI unless performed in the course of complementary chemoembolization. If doubt persists regarding residual malignant tissue, percutaneous fine-needle aspiration biopsy should always be performed.

Complications

Side effects of PEI include transient local pain and fever, especially after injection of large volumes of ethanol. PEI is a safe treatment and serious, procedure-related complications are rare [18]. As with percutaneous fine-needle puncture in general, pneumothorax and hemorrhage are potential but rare complications. Superinfection of necrotic tumor tissue is theoretically possible but has not been found to be a significant concern after PEI. Due to its severe throm-

bogenic effect, ethanol may occasionally induce a portal vein thrombus. Such "chemical" thrombi become visible immediately after PEI (Fig. 8). They are usually reversible and should not be confused with tumor thrombus [3].

Long-term Follow-up

PEI, if performed in limited HCC, enables effective tumor destruction and control of local tumor growth (Fig. 9). The results of recent long-term studies suggest that the overall survival rates after PEI treatment are comparable to those after surgical resection, mainly depending on tumor size and Child's stage of cirrhosis [1–3, 8, 18]. Early observations have suggested that PEI combined with chemoembolization is even more effective than PEI alone [5]. Recurrent manifestations of HCC after PEI may occur locally or in the form of single or multiple intrahepatic secondary lesions (Figs. 4E, F and 6). Needle-tract seeding is an uncommon phenomenon but has been observed after PEI treatment of both HCC and liver metastases [19–21] (Fig. 10).

Summary

Since PEI is a treatment based on imaging techniques, the radiologist should be familiar with the various findings that may be observed after PEI on US, CT, and MR images immediately after treatment and during later follow-up. Although US is well suited for performing PEI, contrast-enhanced CT currently is the most commonly used imaging method to evaluate the effect of PEI. Residual, nodular areas of contrast enhancement correlate well with residual tumor and warrant additional treatment. Although the findings on MR images obtained after PEI are more complex, MR imaging may be used as an alternative to CT.

References

1. Shiina S, Tagawa K, Unuma T, Fujino H, Uta Y, Niwa Y, Hata Y, Komatsu Y, Shiratori Y, Terano A, et al. (1990) Percutaneous ethanol injection therapy of hepatocellular carcinoma: Analysis of 77 patients. AJR 155:1221–1226
2. Livraghi T, Bolondi L, Lazzaroni S, Marin G, Morabito A, Rapaccini GL, Salmi A, Torzilli G (1992) Percutaneous ethanol injection in the treatment of hepatocellular carcinoma in cirrhosis. Cancer 68:925–929
3. Livraghi T, Solbiati L (1993) Percutaneous ethanol injection in liver cancer: Method and results. Semin Intervent Radiol 10:69–77
4. Livraghi T, Vettori C, Lazzaroni S (1991) Liver metastases: Results of percutaneous ethanol injection in 14 patients. Radiology 179:709–712
5. Tanaka K, Nakamura S, Numata K, Okazaki H, Endo O, Inoue S, Takamura Y, Sugiyama M, Ohaki Y (1992) Hepatocellular carcinoma: Treatment with percutaneous ethanol injection and transcatheter arterial embolization. Radiology 185:457–460
6. Livraghi T, Lazzaroni S, Pellicanò S, Ravasi S, Torzilli G, Vettori C (1993) Percutaneous ethanol injection of hepatic tumors: Single-session therapy with general anesthesia. AJR 161:1065–1069
7. Joseph FB, Baumgartner D, Bernardino ME (1993) Hepatocellular carcinoma: CT appearance after percutaneous ethanol injection. Radiology 186:553–556
8. Ebara M, Kita K, Sugiura N, Yoshikawa M, Fukuda H, Ohto M, Kondo F, Kondo Y (1995) Therapeutic effect of percutaneous ethanol injection on hepatocellular carcinoma: Evaluation with CT. Radiology 195:371–377
9. Nagel HS, Bernardino ME (1993) Contrast-enhanced MR imaging of hepatic lesions treated with percutaneous ethanol ablation therapy. Radiology 189:265–270
10. Lencioni R, Caramella D, Bartolozzi C (1993) Response of hepatocellular carcinoma to percutaneous ethanol injection: CT and MR evaluation. J Comput Assist Tomogr 17:723–729
11. Sironi S, De Cobelli F, Livraghi T, Villa G, Zanello A, Taccagni G, DelMaschio A (1994) Small hepatocellular carcinoma treated with percutaneous ethanol injection: Unenhanced and gadolinium-enhanced MR imaging follow-up. Radiology 192:407–412
12. Kadoya M, Matsui O, Takashima T, Nonomura A (1992) Hepatocellular carcinoma: Correlation of MR imaging and histopathologic findings. Radiology 183:819–825
13. Sironi S, Livraghi T, Angeli E, Vanzulli A, Villa G, Colombo E, Taccagni G, DelMaschio A (1993) Small hepatocellular carcinoma: MR follow-up of treatment with percutaneous ethanol injection. Radiology 187:119–123
14. Bartolozzi C, Lencioni R, Caramella D, Falaschi F, Cioni R, DiCoscio G (1994) Hepatocellular carcinoma: CT and MR features after transcatheter arterial embolization and percutaneous ethanol injection. Radiology 191:123–128
15. Bartolozzi C, Lencioni R, Caramella D, Mazzeo S, Ciancia EM (1994) Treatment of hepatocellular carcinoma with percutaneous ethanol injection: Evaluation with contrast-enhanced MR imaging. AJR 162:827–831
16. Lencioni R, Caramella D, Bartolozzi C (1995) Hepatocellular carcinoma: Use of color Doppler US to evaluate response to treatment with percutaneous ethanol injection. Radiology 194:113–118
17. Lee MJ, Mueller PR, Dawson SL, Gazelle SG, Hahn PF, Goldberg MA, Boland GW (1995) Percutaneous ethanol injection for the treatment of hepatic tumors: Indications, mechanism of action, technique and efficacy. AJR 164:215–220
18. Livraghi T, Giorgio A, Marin G, Salmi A, de Sio I, Bolondi L, Pompili M, Brunello F, Lazzaroni S, Torzilli G, et al. (1995) Hepatocellular carcinoma and cirrhosis in 746 patients: Long-term results of percutaneous ethanol injection. Radiology 197:101–108
19. Goletti O, De Negri F, Pucciarelli M, Sidoti F, Bertolucci A, Chiarui M, Seccia M (1992) Subcutaneous seeding after percutaneous ethanol injection of liver metastasis. Radiology 183:785–786
20. Cedrone A, Rapaccini GL, Pompili M, Grattagliano A, Aliotta A, Trombino C (1992) Neoplastic seeding complicating percutaneous ethanol injection for treatment of hepatocellular carcinoma. Radiology 183:787–788
21. Zerbey AL, Mueller PR, Dawson SL, Hoover HC (1994) Pleural seeding from hepatocellular carcinoma: A complication of percutaneous alcohol ablation. Radiology 193:81–82