Ultrasound: Liver tumors yield to ablation techniques

November 01, 2000
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Hepatocellular carcinoma (HCC) is a multicentric malignant tumor. The underlying liver disease of HCC is most often chronic hepatitis or cirrhosis of viral, or less commonly alcoholic, origin. The only method of detecting the tumor before it becomes advanced is screening the patient with ultrasound every six months. Even if the detected tumor is single, other tumors will appear eventually, the time delay depending on various factors.

The natural history of untreated patients has not yet been well established. A retrospective study of cirrhosis patients in Child's class A with single HCC >5 cm in diameter demonstrated a three to five-year survival rate in 11% to 26% of cases. But a prospective study of patients with a more advanced—even if still asymptomatic-tumor demonstrated this survival rate in 18% to 50% of cases.

Orthotopic liver transplantation (OLT) is the only therapy that offers a definitive cure of both the basic disease and HCC in selected patients. Some factors limit or exclude this option:

- shortage of donors compared with the number requested (in Italy, only 150 OLTs are performed each year compared with 10,000 patients);
- high costs and need for advanced technology (HCC is more common in poorer countries);
- stage of disease (patients with simple tumors);
- ethical considerations (in Japan, OLT is not performed, although 25,000 patients per year would be suitable).

Surgical resection, because of the multicentric origin of the tumors, can be only a palliative option. Survival of resected patients varies according to their selection and depends on several prognostic factors. The five-year survival rate of Child's class A patients with HCC 3,4 For many years, transarterial chemoembolization (TACE) of the entire liver was the only option for inoperable patients. Some randomized trials, however, show no significant difference in survival between treated and untreated patients. This is probably due to a counterbalance between local control of the neoplastic tissue and damage to non-neoplastic tissue, which hastens liver insufficiency. TACE is generally performed using the segmental or lobar technique.

Ethanol Injection

Another therapeutic option, percutaneous ethanol injection (PEI), was presented in the Western literature in 1986. The technique was conceived independently at the Vimercate Hospital in Milan and at the University of Chiba in Japan. Ethanol diffuses within the neoplastic cells, causing immediate dehydration of the cytoplasm. It also enters the circulation, causing necrosis of the endothelial cells and platelet aggregation, with consequent necrosis of the small vessels followed by tissue ischemia. The toxic action of ethanol addresses two features of HCC: hypervascularization and the consistency of the neoplastic tissue, which is softer than the surrounding cirrhotic tissue. PEI is performed under ultrasound guidance because real-time control allows faster execution, precise centering of the needle on the target, continuous monitoring of ethanol distribution, and determination of the appropriate quantity of ethanol. The instrument used for the procedure is a 20-cm-long, 21-gauge needle with a closed conical tip and three terminal side holes (PEIT needle,
Radio-Frequency Ablation

RF energy is delivered to the tumor by means of an electrode, a thin (usually 14 to 18-gauge) needle that is electrically insulated along all but the distal 2 to 3 cm of the shaft. When the electrode is connected to the appropriate generator, RF energy emits from the exposed portion. As the energy attempts to reach its electrical ground (a pad placed on the patient's thigh), ion agitation results and the energy is converted into heat. This induces cellular death via coagulation necrosis. Electrodes are placed directly into tumors using CT or, more often, ultrasound guidance. Different RF technologies are available commercially. We prefer to use the so-called cool tip electrode (Radionics, Burlington, Massachusetts, U.S.) connected to a 500-kHz generator, which is made up of a conventional 23-gauge electrode welded into a dual-lumen 18-gauge insulated cannula. This permits internal cooling of the tip with chilled perfusate. Heating of the tissues nearest to the electrode is reduced, thereby preventing tissue carbonization and allowing greater current and power deposition than otherwise achievable with conventional electrodes. Tissue heating and coagulation increases farther from the electrode, while tissues nearest to the electrode are adequately treated because centripetal heat diffusion, following the cessation of perfusion, raises tissue temperatures to >60&degree; C.

During a single session, patients undergo conscious sedation in cases in which one or two electrode insertions are expected (i.e., solitary lesions 20 mm or less). We conducted a randomized trial comparing RF ablation with PEI in the treatment of 86 patients with 112 small HCCs (21 RF resulted in a higher rate of complete necrosis (90% vs. 80%) and required fewer sessions (1.2 vs. 4.8). The study proposed the so-called oven effect (improved heat retention of lesions surrounded by cirrhotic tissue) to explain the amount of induced necrosis, larger than previously observed with metabolic liver tumors. On the basis of the favorable results attained in the initial study, and to take advantage of ongoing technological improvements (cluster electrode, pulsed-current application), we treated 114 patients with 80 medium (3 to 5 cm) or 40 large (5.1 to 9 cm) HCCs. Our experience shows that RF ablation is an effective, safe, and relatively simple procedure. RF obtains higher local efficacy than PEI in HCC 3 cm, RF and PEI are roughly comparable in terms of efficacy. Side effects, complications, and hospital stay favor RF in cases where large amounts of ethanol (>80 mL) would be required in only one session. In cases with a difficult approach or an
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Published on Diagnostic Imaging (http://www.diagnosticimaging.com)

Unfavorable (risk) location, PEI or segmental TACE remain preferable alternatives. In multiple HCC (detectable with ultrasound), RF obtains greater local efficacy than TACE, without its side effects and without impairment of liver function. In some cases, PEI, RF, or segmental TACE can be used in combination.

The following conditions indicate use of PEI or RF ablation:

- The expansive type of HCC initially shows a regional growth, so that a local ablative therapy can be used; or
- Ultrasound screening of a population at risk identifies HCC at an early stage when the tumor is small.

Additional advantages of these therapies include the following:

- PEI and RF do not lose or damage non-neoplastic parenchyma, in contrast with multisegmental resection or whole-liver TACE.
- PEI and RF are low-risk procedures. In published series, the mortality rate is low (0.09% in the largest review study of PEI). Such data are in contrast with the postoperative mortality of surgery: Referral centers report a mortality rate of 0 to 13%, patients selected by ultrasound screening are asymptomatic and, even if untreated, have a life expectancy of more than one year.
- PEI and RF can be easily repeated when new lesions appear, as happens in most patients within five years. Because new lesions reflect the natural history of the disease, the patient should have frequent follow-up so that new lesions can be treated as they form and are still small. The patient can be followed by the same physician in the diagnostic as well as therapeutic phase.
- Low-cost, easy availability of the necessary material (particularly as regards PEI), and the simplicity of the techniques mean that they can be used in many hospitals, even peripheral, without resorting to a referral center.

The large number of patients enrolled in ultrasound screening programs has created demand for an effective, safe, repeatable, and cost-effective treatment that can be made available in many centers. PEI and RF substantially satisfy all such requisites. In the absence of randomized trials, consensus on the indications of the respective therapeutic options remains elusive. Yet extrapolation from retrospective comparative studies and from studies on prognostic factors may prevent useless or even damaging therapies. Although long-term results are not yet available, initial findings anticipate an additional increase in survival achieved with PEI. The treatment of choice for most patients identified by ultrasound screening, excluding candidates for OLT and for surgical partial resection, is indicated as PEI or RF.

OLT and Partial Resection
Few patients have access to OLT. The Liver Cancer Study Group of Japan and other groups have reported factors predictive for a long-term prognosis after partial resection. On multivariate and univariate analysis, the most important prognostic factors were alpha fetoprotein (AFP) level, number of lesions, patient age, lesion size, stage of cirrhosis, margins of resection, portal thrombosis, capsular infiltration, tumor extent, Edmonson-Stainer classification, transaminases level, bilirubin level, and portal hypertension.

Although partial resection assures the highest possibility of complete tumor ablation (and possible satellites if anatomical resection is performed), survival rates after surgery are comparable with those obtained with PEI. This is probably due to a balance of advantages and disadvantages for the two therapies. Results of surgery have also been hampered by an incorrect selection of patients. PEI survival curves are, in fact, always better than curves of resected patients presenting adverse prognostic factors. Additional confirmation of this interpretation is provided in the last report of the
Liver Cancer Study Group of Japan. The three to five-year survival (in Child's A patients with single HCC) Candidates for partial resection should present the following factors:

- **Clinical:** Child's class A, transaminases
- **Technical:** (sub)segmentectomy feasible, postoperative mortality
- **Neoplastic:** small size and number of tumors.

It is still debated whether a complex resection is appropriate for patients without adverse prognostic factors and a small tumor, when the possibility of peritumoral microinvasion is low and the rate of complete ablation with percutaneous ablation techniques is almost 100%. In September 2000, the European Association for the Study of the Liver proposes a randomized trial comparing surgical resection and percutaneous ablation techniques.

In practice, most patients could be managed by the early detection of HCC using ultrasound screening in an at-risk population; treatment with PEI or RF; follow-up with imaging methods and tumor markers (AFP, DCP [des-y-carboxi-prothrombin]); and treatment of new lesions again with PEI or RF.

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**References**


1997;7:514-519.

Disclosures:

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