Minimally Invasive Techniques in the Treatment of Liver Tumors

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Abstract

Background: Despite advances in cancer therapy the treatment of liver tumors remains a challenge. Most patients are poor candidates for surgical resection; both chemotherapy and irradiation have a low success rate and neither is without complications. New minimally invasive techniques for ablation of unresectable tumors have gained attention as effective treatment alternatives. Among these are percutaneous ethanol injection and radiofrequency ablation; both are effective for primary liver tumors and RFA is also effective for hepatic metastases.

Objective: To report our experience with PEI and RFA in the treatment of hepatic lesions.

Methods: The study included 49 lesions in 27 patients: 23 primary lesions in 13 patients treated with PEI and 26 lesions (22 secondary and 4 primary) in 14 patients treated with RFA. PEI was performed on an outpatient basis in the ultrasound suite; RFA was done in hospitalized patients (9 in the ultrasound suite and 4 in the operating room). Patients were followed with triphasic spiral computerized tomography 1 month after treatment and every 3–6 months thereafter.

Results: Complete necrosis was achieved with PEI on the first attempt in 11 of 23 primary lesions (91.3%). In 8.7% (2/23) a second series of treatments was required. Using RFA, complete necrosis was achieved in 85% of lesions (22/26) and partial necrosis in 15% (4/26). Complications included low fever (3 patients), high fever and abscess formation (1 patient), peri-tumoral necrosis (1 patient) and portal vein thrombosis (1 patient).

Conclusions: Our preliminary results confirm that PEI and RFA are an effective and safe option for treating hepatic tumors in patients unfit for surgery.

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Most patients with hepatocellular carcinoma are not candidates for curative therapies such as resection or liver transplantation due to both tumor extension and underlying liver disease [1,2]. Patients with metastatic disease are usually not eligible for hepatic resection due to either the frequent multiplicity of lesions or the relative degree of difficulty of the operation. Furthermore, recurrence of metastatic disease in the postsurgical residual liver is not uncommon and only a minority of such patients are candidates for repeat resection [3,4].

Minimally invasive techniques have recently emerged as alternatives for treatment of non-resectable liver tumors. These include microwave [5], laser [6], radiofrequency ablation [7–13], cryoablation [14], ethanol injection [15–24], and chemoembolization [23–25]. We present our experience with two of these techniques: percutaneous ethanol injection whereby the tumor is ablated chemically, and radiofrequency ablation which causes thermal necrosis. While both techniques are useful for treating HCC, only RFA is effective in metastatic disease. PEI and RFA are widely used worldwide, but we feel they are underestimated in Israel. This report describes our experience with the logistics involved in the introduction of these two minimally invasive techniques and the results in the treatment of 49 hepatic lesions.

Materials and Methods [Tables 1 and 2]

Between October 1999 and December 2001, RFA or PEI was used to treat 27 patients (16 men and 11 women). Their mean age was 62.7 (range 50–78 years). Seventeen had primary and 10 had secondary hepatic tumors. PEI was used in 13 patients and RFA in 14. One patient received both PEI and RF (on two different occasions).

Most of the primary tumors were HCC (16/17), all associated with advanced cirrhosis. A single patient, a 32 year old woman, who was operated on for a large bleeding 10 cm adenoma, was also treated with intraoperative RFA for an additional 5 cm adenoma. All HCC lesions were histologically diagnosed by percutaneous ultrasound-guided biopsy. The mean size of the HCC lesions treated by PEI was 2.7 cm (range 1.0–5.0 cm). Metastatic lesions were most frequently due to colon carcinoma (8 of 10 patients); breast and prostate carcinoma were the etiologies in the remainder. All 10 patients with metastatic disease underwent resection of the primary tumor. In 5 of the 10 a partial hepatic metastasectomy was also performed 6–18 months prior to RFA. The mean secondary lesion diameter was 2.0 cm (range 1.0–5.5 cm). The mean number of secondary tumors per patient was 2.5 (range 1–4). Follow-up imaging was performed with triphasic spiral CT at 1 month and 3 months following treatment and every 3–6 months thereafter. Lack of enhancement on both arterial and portal phase was considered suggestive of complete necrosis. One patient was followed with gadolinium-enhanced magnetic resonance imaging due to contrast material allergy. Follow-up Doppler ultrasound was performed to assure the patency of the hepatic blood vessels. Three patients underwent liver transplantation 1 month to 1 year post-PEI treatment.

PEI technique

PEI was performed under ultrasound guidance in multiple sessions. Skin preparation and local anesthesia are the only requirements of this procedure. Sterile 95% ethanol was injected into the tumor

RFA = radiofrequency ablation
PEI = percutaneous ethanol injection

HCC = hepatocellular carcinoma

Table 1. PEI in 13 patients with 23 lesions

Patient/ Age (yr)	Gender	Cirrhosis	HCC: No. of lesions	HCC: diameter (cm)	No. of sessions	Complete necrosis on follow-up CT (months): positive or negative	Clinical course	Complications
1/50	F	+hepatitis	1	2	4	1–9 mo: pos	Transplantation (1 yr)	
2/59	M	+hepatitis	1	4.5	8	1–3 mo: pos	Transplantation (4 mo)	
3/60	M	+hepatitis	1	4.5	8	1 mo: pos	Transplantation (2 mo)	Fever on 2nd day (resolved)
4/70	M	+hepatitis	1	4	Series 1:7 Series 2:4	1 mo: neg 2–18 mo: pos	2 new lesions (3 mo). RFA [Table 2#1]	Fever on 2nd day (resolved)
5/75	F	+hepatitis	2	1.5, 2	4	1–3 mo: pos	3 new lesions (3 mo), ascites stopped. Died (6 mo)	
6/78	M	+hepatitis	1	2	4		1–18 mo: pos	2 new lesions (12 mo). 2nd PEI
		2nd PEI	2 new	1.5, 2	5			Fever on 2nd day (resolved)
7/67	F	+hepatitis	1	2.6	4	1–12 mo: pos		
8/63	M	+hepatitis	1	4	7	1–12 mo: pos		
9(A)/68	M	+hepatitis	2	2.8	5	1–18 mo: pos	2 new lesions (18 mo). 2nd PEI	+ PVT (resolved)
		2nd PEI	2	1.5, 2		2		
10(A)/70	M	+alcoholic	2	1.5, 3		Series 1:6 Series 2:5	1 mo: neg 2–18 mo: pos	3 new lesions (18 mo). 2nd PEI
		2nd PEI	3	1.5, 2, 3	6			
11/60		F	+hepatitis	1	2.5	6	1–3 mo: pos	
12/65		F	+hepatitis	1	3	7	1–3 mo: pos	
13/68		M	+hepatitis	2	2.4,3. 2	7	1–6 mo: pos	

under continuous real-time sonographic monitoring. Treatment was terminated when all areas of the tumor became echogenic on sonography due to bubble distribution within the tumor. Treatment time was approximately 30 minutes [Figure 1].

RFA technique

All procedures were performed under ultrasound guidance with continuous sonographic monitoring. Ten patients were treated in the ultrasound suite under deep intravenous sedation. Four

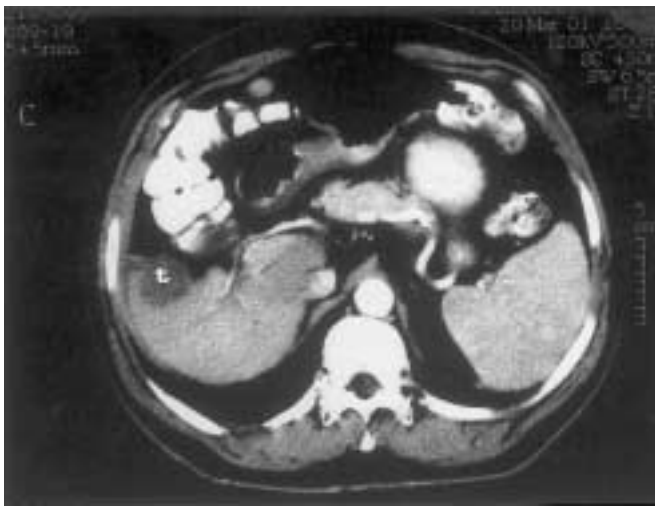

Figure 1. Demonstrates the tumor (t) in the right lobe of the liver. PEI: 95% ethanol is Post-PEI follow-up CT demonstrates a completely hypo-attenuated tumor (t) indicating complete ablation.

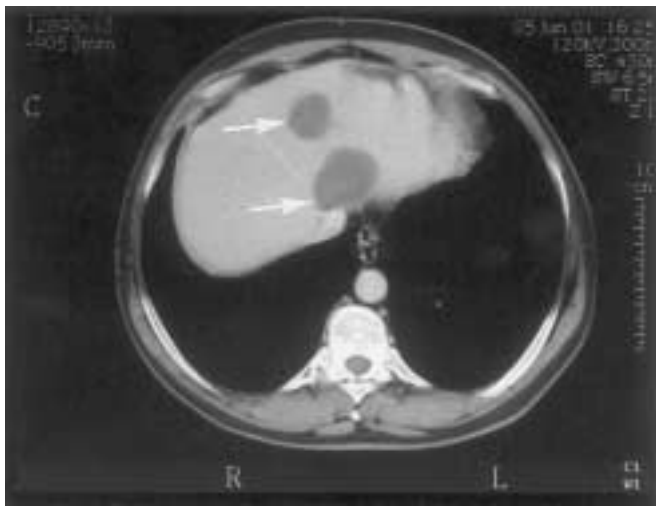

Figure 2. Arterial phase spiral CT pre-RFA (arrows). Laparoscopic RFA under ultrasound Post-RFA follow-up CT demonstrates the two lesions (arrows) totally hypoechoic, non-enhancing, consistent with total necrosis.

Table 2. RFA in 14 patients with 26 lesions

Patient/ Age (yr)	Gender	Primary tumor	No. of tumors	Tumor diameter (cm)	Mode of procedure	Complete necrosis on follow-up CT (months): positive or negative	Clinical course	Complications
Liver tumors: Primary								
1/70	M	Cirrhosis: HCC	2	3, 1.5	Laparoscopic	1–6 mo: pos		
2/50	M	Cirrhosis: HCC	1	3	Laparoscopic	1 mo: pos		
3/52	F	Cirrhosis: HCC	2	1 , 5	Percutaneous	1 mo: pos		
4/32	F	Adenoma*	1	5	Intraoperative (open)	1–9 mo: neg		
Liver tumors: Secondary								
1/60	M	Colon s/p right hepatectomy	1	2	Percutaneous	1–18 mo: pos	1 new lesion (18 mo), chemotherapy	Bile duct injury (focal) **
2/62	M	Colon s/p right hepatectomy	1	5.5	Percutaneous	–	Chemotherapy	
3/75	F	Colon	3	2, 3, 3	Intraoperative (open)	1–12 mo: neg	2 new lesions (12 mo), chemotherapy	
4/60	F	Colon s/p right hepatectomy	1	2	Percutaneous	–	Metastasectomy	
5/82	F	Colon	3	1, 1, 2	Percutaneous		1–12 mo: pos	
6/60	M	Colon s/p right hepatectomy	1	5.0	Percutaneous	–	New lesion (1 mo), chemotherapy	2nd week fever abscess, formation, drainage***, seeding along catheter tract
7/82	M	Colon	2	1.5, 2	Percutaneous	1 mo: pos		
8/50	M	Colon s/p right hepatectomy	1	3	Percutaneous	1–3 mo: pos		
9/35	F	Breast	4	1.5, 2,3,5	Percutaneous	1–3 mo: pos	Deceased (1 yr)	
10/68	M	Prostate	3	1.7, 2, 4	Percutaneous	1–12 mo: pos		Fever on 4th day (resolved)

* Three large adenomas in the liver, one post-internal bleeding: two underwent surgical resection, one RFA due to its location (seg. 8)
** Too large (7 cm) necrotic area was shrunk to 2 cm and resolved, causing localized bile duct fibrosis and segmental dilatation.
*** Abscess drained due to unresolved fever.

patients were treated in the operating room under general anesthesia. In two cases, laparoscopic RFA was performed due to the inaccessible location of the tumor for percutaneous treatment. In the other two, RFA was performed during open surgery, together with another procedure (colectomy, partial hepatectomy). In most cases (13/14 patients) a cooled-tip 18 gauge single electrode (Radionics, Burlington, MA, USA) was used. In one patient a 6-hook array umbrella-shaped electrode was used (Radiotherapeutics, Sunnyvale, CA, USA).

The response of the tumor to the thermal injury (coagulative necrosis) was manifested sonographically as a hyperechoic area, which initially surrounds the electrode tip and subsequently expands to a spherical area of 2.3 cm [Figure 2]. The number of electrode insertions and ablation cycles were subject to tumor diameter.

The edges of adjacent areas of necrosis should overlap. Total treatment time varied between 2 and 4 hours depending on the size and number of lesions.

Results

PEI ablation

Complete necrosis after the first treatment was achieved in 21 of 23 lesions (91.3%), as confirmed by CT. In two lesions (8.7%) CT demonstrated an area of residual enhancement, suggestive of only partial necrosis. Therefore an additional PEI was performed, which resulted in complete necrosis, as confirmed by the next follow-up CT. In all three transplanted patients the lesion in the resected liver was found to be completely necrotic on histologic examination. Among the 10 patients who did not undergo liver transplantation the treated lesions remained completely necrotic at last follow-up of 3–18 months. Five patients (50%) developed new HCC tumors (11 lesions) 3–18 months after the first PEI treatment and were retreated with PEI or RF.

- *Complications*. Three patients developed transient fever (38–39°C) that resolved after several days. One patient had transient portal vein thrombosis that resolved after 2 months without anticoagulant therapy.

- *Outcome*. All but one patient in this group are alive between 1 month and 2 years post-treatment. One patient died due to worsening of cirrhosis not related to the treatment [Table 1, patient 5].

RF ablation

One month follow-up CT examination revealed complete necrosis in 22 of 26 lesions (85%) and partial necrosis in 4 lesions (15%). The follow-up period ranged from 1 to 18 months. Local tumor recurrence was not observed in any of the treated patients in whom total necrosis was achieved. However, new lesions were noted in two of these patients and they were treated successfully with chemotherapy. Among the patients with partial necrosis, one had metastasectomy of the residual tumor and two patients were treated with aggressive chemotherapy. The fourth patient was the adenoma case that was not retreated due to its benign nature.

- *Complications*. One patient developed transient fever (38°C) that resolved after 3 days. Another patient developed high non-resolving fever due to abscess formation at the treated lesion site, necessitating percutaneous catheter drainage [Table 2, patient 6]. One patient developed a large post-treatment necrotic area, without fever, which shrank gradually over 6 months into a localized fibrotic region.
- *Outcome*. In this group also only one patient died due to development of multiple extrahepatic metastases [Table 2, patient 9].

Discussion

The incidence of hepatocellular carcinoma is increasing in the western world due to the increasing incidence of cirrhosis. Patients with HCC are often poor candidates for surgical resection due to reduced hepatic reserve and the tendency to develop new tumor nodules in the residual liver.

PEI has been demonstrated to be a safe, effective, repeatable, easy to perform and inexpensive therapy for completely ablating small HCC lesions and improving long-term survival [15–18]. For larger lesions, PEI may be performed in tandem with transcatheter chemoembolization [23,24]. Two factors are believed to influence the efficacy and safety of PEI for treating HCC: a) the difference in consistency between the firm cirrhotic surrounding tissue and the softer neoplastic issue favors the diffusion of the ethanol within the tumor only; and b) the hypervascular nature of HCC and the presence of arteriovenous shunting in the tumor favor uniform and selective distribution of the ethanol within the tumor.

The size criteria for optimal selection are a single lesion no greater than 5 cm in diameter or two to three lesions no larger than 3 cm each. The post-treatment evaluation requires triphasic contrast-enhanced CT or MRI. Complete necrosis is indicated by lack of enhancement within the treated lesion. If residual enhancement is detected, repeat PEI directed to this region is indicated to achieve complete ablation [19,20].

The reported survival rate post-PEI is comparable to that of surgical resection, suggesting that the higher complete removal rate of surgery is balanced by the early higher morbidity and long-term reduction in hepatic reserve. In our series, complete necrosis was achieved in all treated lesions after one (91.3%) or two (8.7%) sessions. Most patients experienced local pain during the alcohol injection, while several patients experienced right shoulder pain in the first hour after the procedure, all of which were controlled by mild analgesia. Three patients had low grade fever (38–39°) that resolved after 2–3 days. The fever is thought to result from the release of pyrogenic substances from the necrotic tissue [15,16]. One patient had transient portal vein thrombosis, which resolved after 2 months; this is thought to reflect ethanol-induced chemical thrombosis in a portal tributary. All treated lesions in the 10 patients who did not proceed to liver transplantation remained completely necrotic on follow-up CT scans at 3–18 months. New lesions were found in five of these patients after 3–18 months. The development of new HCC lesions in cirrhotic patients is characteristic of the disease and is not evidence of tumor seeding as previously reported [15–18]. No new lesions arose in the needle tract, presumably due to reflux of alcohol along the tract.

Radiofrequency ablation is a promising new minimally invasive technique for the treatment of hepatic tumors [7–13]. This technique utilizes high frequency alternating current to heat tissue to the point of coagulation necrosis. With a conventional radiofrequency electrode the diameter of the necrosis resulting from a single insertion is 1.6 cm. Therefore, multiple overlapping electrode insertions are necessary for adequate treatment of lesions. Cooled-tip electrode reduces tissue charring, thus allowing a larger area of necrosis [9,10].

The selection criteria include disease that is confined to the liver and not more than three to four lesions. Lesions of 5 cm or larger require specially designed needles and newer techniques. RFA improves survival in cirrhotic patients, in Childs' class A and B with HCC but not in Childs' class C patients [10]. The side effects of RFA during the procedure include pain, fever and pleural effusion. Pain is controlled by deep intravenous sedation or general anesthesia, necessitating the presence of an anesthesiologist. Fever and pleural effusions are usually reactive to the necrotic process and are self-limiting. Pleural effusion is most likely to follow ablation of tumors in the dome of the liver. A potentially serious complication of RFA is thermal necrosis of adjacent organs. This may occur when the tumor is inseparable from the gallbladder, stomach or porta hepatitis structures. Blood vessels are not at risk of injury due to the cooling effect of flowing blood. However, this cooling effect may prevent a portion of tumor adjacent to large blood vessels from becoming completely ablated, as occurred in three of our patients. Careful ablation of the needle tract should be performed to control hemostasis and to avoid tumor seeding, which may be a serious complication, as described by Lovet et al. [13]. In our experience, the only case of tumor seeding was along the drainage catheter tract, which was placed in the abscess that developed post-RFA [Table 2, patient 6]. Therefore, drainage catheters should be avoided as far as is clinically possible.

In our series, 26 lesions were treated by RFA. Complete necrosis was achieved in 22 lesions (85%) and partial necrosis in four others (15%). Three of the four lesions with partial necrosis were the largest lesions in our series (5.0–5.5 cm), and the residual tissue was adjacent to large blood vessels. In the fourth lesion, although

relatively small, the residual tissue was also adjacent to the portal vein. Our preliminary results demonstrate and confirm that PEI and RFA are safe and effective minimally invasive alternatives for patients with hepatic tumors in whom surgery cannot be considered as a reasonable therapeutic option.

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Capsule

Cell-free hemoglobin limits nitric oxide bioavailability in sickle cell disease

Although the deleterious vasoconstrictive effects of cell-free, hemoglobin-based blood substitutes are known, the systemic effects of chronic hemolysis on nitric oxide (NO) bioavailability have not been considered or quantified. Central to this investigation is the understanding that NO reacts at least 1,000 times more rapidly with free hemoglobin solutions than with erythrocytes. Reiter et al. hypothesized that decompartmentalization of hemoglobin into plasma would divert NO from homeostatic vascular function. They demonstrate that plasma from patients with sickle cell disease contains cell-free ferrous hemoglobin, which stoichiometrically consumes micromolar quantities of NO and abrogates forearm blood flow responses to NO donor infusions. Therapies that inactivate plasma hemoglobin by oxidation or NO ligation restore NO bioavailability. Decompartmentalization of hemoglobin and subsequent dioxygenation of NO may explain the vascular complications shared by acute and chronic hemolytic disorders.

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