Tumor Cell Seeding During Ethanol Injection Therapy for Hepatocellular Carcinoma under Ultrasound Guidance

Toshihiko Kurohiji*, Yuichi Yamashita** and Takayuki Shirakusa**

*Department of Surgery, Shin Koga Hospital,
**Second Department of Surgery, Fukuoka University Faculty of Medicine

Abstract: Percutaneous ethanol injection therapy (PEIT) is now widely accepted for patients with a small hepatocellular carcinoma (HCC) as an alternative to a surgical resection of HCC, since PEIT is minimally invasive, simple and easy. However, PEIT is not entirely free from complications. Several cases of tumor cell seeding through the needle tract following PEIT as one type of complication have been reported. We have also experienced three cases of tumor cell seeding. Two were treated with PEIT in our hospital and the other was treated at another hospital. The site of a metastasis was in the chest wall in two patients, and in the abdominal wall in the other case. Since 1992, we have experienced 198 patients with HCC treated with PEIT. The incidence of the tumor cell seeding in our series was 0.08% (2 of 2485) sessions of PEIT occurring in 1.01% (2 of 198) of the patients.

Careful attention should be paid to the appearance of needle tract seeding following PEIT for HCC to detect such instances of metastasis, and informed consent concerning the incidence of such metastasis should be also to be obtained.

Key words: hepatocellular carcinoma, percutaneous ethanol injection therapy, needle tract seeding complications

Introduction

Percutaneous ethanol injection therapy (PEIT) is now widely recognized as a low-invasive and effective therapy for hepatocellular carcinoma (HCC). Many patients with HCC have been successfully treated by this treatment over the past ten years in Japan. On the other hand, several cases of tumor cell seeding through the needle tract following PEIT or fine needle aspiration biopsy (FNAB) have been reported. However, there has been no report of data on the incidence rate of such tumor seeding. We herein report our experience of patients with tumor cell seeding of HCC and the incidence rate of such metastasis in our series.

Patients and Results

From May 1st 1992 through September 31st 2000 we experienced 198 cases of hepatocellular carcinoma treated with PEIT in Shin Koga Hospital. These included 115 patients with primary HCC and 83 patients with post-operative recurrence in the liver. The characteristics of these patients and of the injection are listed in Table 1. 2485 sessions of PEIT were performed during this series, and we experienced two patients with a tumor cell seeding in the needle tract following PEIT who were treated with PEIT at our
hospital. In addition, we also experienced another one patient who had been treated at another hospital. Prior to PEIT, FNAB was performed to determine the diagnosis in one of those three cases. The site of a metastasis was in the chest wall in two patients, and in the abdominal wall in the other case.

Cases (Table 2)

Case 1: A 62-year-old male patient. He received PEIT of 3 sessions for a tumor of 15 mm in size in the anterior superior subsegment after FNAB in April 1992. He had again received PEIT of 5 sessions for another tumor (28 mm in size) in the lateral segment in April 1997. The total amount of injected ethanol was not clear because he was treated in other hospital. In November 1997, an abdominal CT revealed a tumor measuring 11 mm in size located in the upper abdominal rectal muscle. Tumor extirpation was performed at three months after the last session of PEIT. An abdominal wall tumor was pathologically confirmed to be metastasis from the HCC. The location was along a needle tract of the PEIT. This tumor was removed surgically. A pathological examination confirmed this chest wall tumor to be metastasis from HCC. This patient is alive with new intrahepatic recurrence and pelvic bone metastasis at 33 months after the extirpation.

Case 2: A 72-year-old female. She underwent a surgical resection of an HCC in the anterior inferior subsegment of the liver in July 1992. Thirty-two months after the operation, an intrahepatic recurrence measuring 20 mm in size in the posterior inferior subsegment of the liver was detected. PEIT consisting of 9 sessions was immediately performed in an out-patient clinic. A total volume of 26 ml ethanol was injected. Thirteen months after PEIT, another intrahepatic recurrence in the anterior superior subsegment was detected by ultrasound, and PEIT of 4 sessions was performed again. FNAB was not performed at this time. Three months later, a new low echoic lesion measuring 9 mm in size was found by ultrasonography in the 10th inter-costal region. Chest wall tumor seeding through a tract of last PEIT was strongly suspected, and this tumor was removed surgically. A pathological examination confirmed this chest wall tumor to be metastasis from HCC. This patient is alive with new intrahepatic recurrence and pelvic bone metastasis at 33 months after the extirpation.

Case 3: A 72-year-old female was diagnosed to have HCC in the posterior superior subsegment of the liver on March 1996. The lesion measured 28×21 mm in diameter. PEIT consisting of 5 sessions was performed after FNAB using a 22G needle, and a total of 18 ml ethanol was injected. However, the serum araphetoprotein (AFP) level did not decrease to within the normal limits. Transarterial embolization (TAE) was thus subsequently performed. The serum AFP level increased again at eleven months after TAE. A subcutaneous tumor on the right lateral chest wall was found by ultrasonography at 15 months after the last session of PEIT. This lesion was located in the previous needle tract of the PEIT. This tumor was considered to be due to tumor cell seeding of the HCC caused by PEIT. Both the primary

Table 1. Patient characteristics

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>198</td>
</tr>
<tr>
<td>Age (years)</td>
<td>66.1±7.1</td>
</tr>
<tr>
<td>Male/Female ratio</td>
<td>2.2</td>
</tr>
<tr>
<td>Total No. of sessions</td>
<td>2485</td>
</tr>
<tr>
<td>No. of tumor nodes</td>
<td>509</td>
</tr>
<tr>
<td>Diameter of tumor (mm)</td>
<td>1.9±1.3</td>
</tr>
<tr>
<td>Ethanol volume/session (ml)</td>
<td>2.1±0.8</td>
</tr>
<tr>
<td>Total volume of ethanol injected per node (ml)</td>
<td>9.5±7.3</td>
</tr>
</tbody>
</table>
Fig. 1. A resected specimen of chest wall metastasis in case 3. The metastatic lesion (arrow) was resected with adjacent tissue. Bleeding area is seen in the lesion.

Fig. 2. Histology of venous invasion in metastatic lesion of case 3. Venous and lymphatic invasions are seen around metastatic lesion. The arrows show venous invasion. (×20)
tumor and the chest wall metastasis were simultaneously removed (Fig. 1). The resected metastasis showed venous and lymphatic invasion (Fig. 2). But no viable tumor cells were microscopically observed in the resected primary tumor. At three months after the operation, multiple lung metastases was detected on chest X-ray film with an elevation of serum AFP level. Despite of the systemic chemotherapy with 5-FU and CDDP, she died of lung metastasis from HCC at +1 months after the operation and at - months after PEIT.

**Pathological findings**

The histological classification of the primary lesion by FNAB or a surgical resection was moderately differentiated HCC in all 3 cases. The site of metastasis in the chest wall or abdominal wall was moderately to poorly differentiated HCC in 2 cases (Case 1 and 3), and moderately differentiated HCC in the other (Case 2) (Table 2).

**Clinical characteristics**

According to the imaging findings, all three primary lesions and all three metastatic lesions appeared as low echoic images on US (Fig. 3), as positive on dynamic enhancement CT (Fig. 4), and demonstrated a rich arterial blood supply on angiography.

The durations from PEIT until the detection of the metastasis of tumor seeding were 3 months in Cases 1 and 2, and 15 months in Case 3 (Table 2).

The prognoses of those three patients were as followings: Patient of Case 1 died at 32 months after the PEIT and at 17 months after PEIT.

**Table 2.** Summary of three patients with HCC having a seeded tumor in a needle tract of PEIT

<table>
<thead>
<tr>
<th>Case</th>
<th>histology of Primary HCC</th>
<th>histology of seeded tumor</th>
<th>Duration from PEIT to detection of seeded tumor</th>
<th>Prognosis after resection of seeded tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. 62y M</td>
<td>mod.</td>
<td>mod.~poor.</td>
<td>3 months</td>
<td>34 months alive with IM</td>
</tr>
<tr>
<td>2. 72y F</td>
<td>mod.</td>
<td>mod.</td>
<td>3 months</td>
<td>33 months alive with IM, BM</td>
</tr>
<tr>
<td>3. 72y F</td>
<td>mod.</td>
<td>mod.~poor.</td>
<td>15 months</td>
<td>17 months death of LM</td>
</tr>
</tbody>
</table>


**Fig. 3.** Ultrasonogram of chest wall metastasis in case 3. The metastatic lesion covered with a capsule shows hypoechoic (arrow).
after a simultaneous resection of the primary lesion and the metastasis. Both of the other two patients are still alive with metastases (Table 2).

Incidence of tumor seeding

The incidence of tumor seeding in our series was 0.08% (2 of 2485) sessions of PEIT occurring in 1.01% (2 of 198) of patients.

Discussion

PEIT for small HCC is widely accepted, especially for tumors measuring less than 3 cm in diameter, and is well accepted as a treatment of first choice in Japan because of its safety and its low-invasiveness. According to a follow-up study by the Liver Cancer Study group of Japan, the resectability of HCC is 34.4%. This low rate is mainly due to the poor liver function because HCC in Japan commonly associated with liver cirrhosis or chronic hepatitis, and only 5.8% of HCC are coexistent with a normal liver. Therefore, PEIT has become the treatment of first choice for patients with a small HCC having liver cirrhosis. Recently, the number of HCC patients treated with PEIT has increased. At the same time, the technological progress of ultrasound field enabled finding smaller tumors measuring less than 1 cm in diameter in a cirrhotic liver. Patients with a hepatitis C virus are well recognized to be a high risk group for HCC. More precise imaging of the tumor can be obtained with ultrasonography during the follow-up series in those patients. When a tiny lesion measuring less than 1 cm in size is depicted by ultrasonography, it is not easy to determine optimal treatment modality. 1 cm is not large enough to be identified by CT, MRI or Angiography. In examining these very small lesions, FNAB under ultrasound guidance is an indispensable diagnostic procedure for a histo-pathological confirmation. However, several types of complications with this technique have been reported. These complications include pain and fever either after or during the
treatment, bile leakage or hemorrhaging from the puncture site of the liver surface, vasovagal attack, and tumor cell implantation.\textsuperscript{18-21}

The most crucial complication may be tumor cell seeding through the needle tract among all of these complications. This has been well recognized in the history of the FNAB for various types of tumors not only in the abdominal cavity, but also in the thoracic cavity and in the prostate. Sakurai et al\textsuperscript{30} first described a case report about tumor cell implantation after FNAB for HCC in 1983. Since then similar reports have followed from Italy as well as Japan after FNAB and/or PEIT. Our cases also supported those reports. According to these reports, there has been no correlation between the duration and tumor size. In general, a tumor-seeding tendency may be related to the malignancy potential of the primary tumor. Based on a review of the literatures, including our cases, histological classification of the primary HCC was mainly moderately differentiated type or poorly differentiated type.

Though Kimura et al\textsuperscript{35} reported a case of lymph node metastasis after PEIT which resulted in death, no report described tumor seeding as the main cause of death. The histological findings of a chest wall metastasis in our case 3 revealed massive tumor thrombosis in the lymphatic duct. Though complete necrosis in primary tumor was noted, and no intrahepatic recurrence was detected at the time of death, this patient considered to have died due to metastasis caused by needle tract tumor cell seeding.

According to our data, the tumor-seeding incidence per patient was 1.01%. If we introduce this incidence to the number of patients\textsuperscript{37} treated by PEIT in Japan. The number of tumor-seeding cases may be almost 30 patients per year. There is therefore a large difference between the number of the patients actually reported and this hypothetical number. The reason for this may be due to the fact that physicians do not report all complications, and that some may also dismiss the tumor seeded site. We have to understand the benefits and the side effects of this useful treatment modality. At the time when we choose the treatment strategy, or diagnostic procedure, the correct indications for each tumor must be selected. Then if a puncture procedure is necessary, then full attention should be paid to avoid tumor seeding. Careful observation along the needle tract should be done during follow-up. In addition, any unnecessary needle punctures into a tumor in the liver should also be avoided.

References


(Received on September 3, 2001, Accepted on December 26, 2001)