guided percutaneous ^{125}I seed implantation brachytherapy. The study was conducted in accordance with the guidelines of the Regional Ethics Committee for conducting research involving humans. Each subject or his/her relative/caregiver provided signed consent to participate in the treatment.

M

M : The materials required by the ^{125}I radioactive seed implantation included 18G seed implantation needle, implantation gun and ^{125}I radioactive seed, all provided by Ningbo Junan Pharmaceutical Technology Co., Ltd.

^{125}I seed has a half-life of 59.6d, an energy of 27.4~31.4 Kev (X ray) and 35.5 Kev (ray), and an activity of 0.6~0.8 mCi per seed. The matched peripheral dose is 120~150 Gy. The seeds were

- no change (NC): the product decreases by <50% compared to that before treatment, and the active area reinforcement shows no significant abatement, or the product increases by <25%
- progress disease (PD): the product increases by ≥ 25% compared to that before treatment, and the active area reinforcement scope expands, and new active areas appear in periphery [3]

All patients received the follow-up visits lasting a period ranging from 2 to 12 months and their liver functions were assessed before and after operation according to Child-Pugh grading criteria. After that, we continue our telephone follow-up. The median telephone follow-up was 48 months (range, 36-60 months).

The complications were scored using the Radiation Therapy Oncology Group (PTOG)/European Organization for Research and Treatment of Cancer (EORCT) late radiation morbidity score [6].

The survival time was calculated from the date of implantation to the last date of follow-up or date of death. In these calculations, deaths due to any reason were scored as events. Local control was defined as lack of tumor progression either in or adjacent to the implanted volume. The overall local control and survival times were determined using the Kaplan-Meier method by using SPSS12.0 for Windows (SPSS, Chicago, IL).

R

I

In our research group, 26 patients survived in 3 months after seeds implantation; the CT or MRI examination performed on them showed that 26 patients had 31 focuses, of which 3 reached CR, 21 PR, 5 NC and 2 PD; according to the 3-month follow-up visit assessment, 1 focus appeared to be progressive, which reached PR in 3 months after implantation of additional seeds (Figure 1).

3 patients out of the group were not re-examined in 3 months after seeds implantation but re-examined in 6 months; the CT or MRI examination performed on them showed that they had 3 focuses, of which 1 reached CR, 1 PR, 1 NC and 0 PD.

As a result, the 29 patients of the group had 34 focuses and the imaging evaluation performed on them in 6 months after operation showed that 4 focuses reached CR (11.8%), 23 PR (67.6%), 6 NC (17.6%) and 1 PD (2.9%), and that the total effective rate (CR+PR) reached 79.4%. According to the focus size, the 34 focuses were divided into 3 grades for respective assessment of therapeutic effect. The assessment results were as shown in Table 1. The above patients showed no significant migration of radioactive seeds.

Liver functions before and after operation 29 patients were assessed before and after operation according to Child-Pugh grading criteria. Before the operation, 16 patients belonged to grade A, 13 grade B and 0 grade C; after the operation, the conventional liver protection treatment was performed, and 26 patients were assessed once again in terms of liver functions in 3 months after operation. The assessment result showed that 4 patients who had belonged to grade A now belonged to B and 1 who had belonged to grade B now belonged to grade C. 29 patients were assessed once again in terms of liver functions in 6 months after operation. Compared with the data gained in 3 months after operation, 4 patients who had belonged to grade A now belonged to B, and 2 who had belonged to grade B now belonged to grade C. Among those who belonged to grade C, 1 patient had a single focus ≤ 3 cm but many sub-focuses inside it; 2 patients had focuses >5 cm, one having progressive focus according to imaging evaluation, the other one having many sub-focuses in other parts of liver. The remaining patients basically belonged to grade A or B.

Time-based variance in focus size 26 out of 29 patients received continuous follow-up visits in 2 to 6 months after operation. The follow-up visit results showed that 25 of 31 focuses reached CR or PR according to the imaging assessment results, and that their focuses shrank with time. Specifically, in 2 to 3 months after operation, 3 focuses reached CR and 3 PR; in 3 to 4 months after operation, 1 out of the remaining focuses reached CR and 15 PR; in 4 to 5 months after operation, 4 focuses, each with a size >5 cm, shrank significantly.

So far, 15 patients had died. The median overall survival time was 23. 14.8 months for all patients, and the 1, 2 and 3-year survival rate was 85.4%.

C

Two patients had grade 1 skin reaction, one experienced grade 1 mucosal reaction. We did not observe blood vessel damage and neuropathy in the patients.

D

Hepatic Carcinoma (HCC) is a severely malignant tumor of which the cells proliferate rapidly in their short life. A normal liver is a radiosensitive organ. Studies have shown that 75% patients show hepatic insufficiency if external exposure is >30 grays (Gy). External beam irradiation therapy for HCC has been used infrequently in part because of the limited tolerance of the entire liver (30 Gy), which is insufficient to control macroscopic disease [7]. The external radiation therapy for hepatic carcinoma has been reported to lead to some serious complications such as radiation hepatitis, radiation pneumonia, pulmonary embolism, pulmonary fibrosis, gastroduodenal ulcer and arrest of bone marrow. The application of chemotherapy drugs decreases the radiation tolerance of liver, and more than 80% patients with primary hepatic carcinoma have a significantly lowered hepatic radiation tolerance due to their combination with cirrhosis at various degrees. This is also one of the reasons why the conventional radiotherapy has a poor therapeutic effect [8-12]. The CT-guided percutaneous permanent radioactive seed implantation as a supplement to operation, chemotherapy and radiotherapy is increasingly valued in treatment of hepatic malignant tumor. The radioactive seeds that are implanted in tumor can continuously emit ray which multiplies the radiation effect of tumor cells and so continuously radiate and destroy the DNA double strands of tumor karyon to lead to loss of reproductive ability of tumor cells; in addition, unlike external radiation, the radioactive seed implantation therapy doesn't cause systemic complications and therefore influences the liver functions to a lighter extent. Among the patients in our research during the follow-up visit, most kept their liver function Child-Pugh grade at B or above, and the only 3 whose grade impact on the liver functions.

Compared with the three-dimensional conformal radiotherapy, the solution in our research has a better therapeutic effect and lighter adverse reaction. Through analysis, the reasons include:

- The sensitivity of tumor cells to rays differs in time phase; the DNA post-synthetic phase and the karyokinesis phase are the sensitive phase in which a few rays can destroy the reproductive ability of tumor. The sensitivity is poor in other time phases, especially in the stationary phase in which the cells are insensitive to rays [13,14]. The [illegible] short-term radiotherapy can only kill the tumor cells of sometime phases. ^{125}I radioactive seed implantation brachytherapy can continuously act on tumor cells and kill or hurt tumor stem cells. Enough doses and enough half-life of seeds can make all tumor cells lose their reproductive ability so as to heal patients [15].
- The three-dimensional conformal radiotherapy does not only kill and wound tumor through the focusing effect of rays, but also hurts the peripheral tissues. The effective damaging radius of radioactive seed is small, ranging from 0.5 to 1.0 cm, consequently causing less damage to peripheral normal tissues.

Through the therapeutic effect observation given to tumors in various sizes, we found that a focus can reach CR or be very likely to reach PR when it is ≤ 5 cm, and that the majority of the focuses which are >5 cm may reach PR. In general, most patients reached PR. Even if the radioactive seeds were arranged to surround the tumor and the target volume dose based on the calculation by TPS met the requirement of therapeutic dose, the therapeutic effect still varied due to the following reasons:

- different pathological types of tumors had different sensitivities to radiotherapy, which may be the main reason
- unexpected factors appeared during operation influenced the arrangement of seeds in a way against the plan
- big tumor constantly shrank in the course of operation, but different shrinkage of each part of it led to a changed target volume and a less even dose distribution

Moreover, according to the imaging-based evaluation of therapeutic effect, we found that there were continuous enhancement zones at various degrees around the seeds of most patients, instead of apparent fast-in-fast-out symptoms (Figure 2). We believe that this was closely related to radioactive damage. After a liver is radiated, its endothelial cells are first damaged; subsequently, the liver will suffer central vein occlusion, then local hepatic dropsy and finally hepatic fibrosis. Usually 1 to 4 months are required to observe such hepatic variations caused by the radioactive damages after the liver is radiated, which is consistent with the follow-up visit time spent by us.

According to our observation given to time-based variations in tumor size, we found that the tumors of those patients who reached CR or PR shrank significantly in 3 or 4 months after treatment. The reasons