



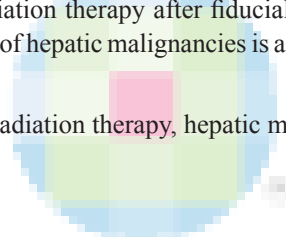
Sonographic-guided Percutaneous Fiducial Marker Implantation of Hepatic Malignancies for CyberKnife Radiation Therapy: Evaluation of Safety and Technical Efficacy

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Background: CyberKnife radiation therapy has a widely used system in the treatment of extracranial lesions. Implanting gold fiducial markers around a tumor is an important procedure for the planning and aiming of CyberKnife radiation therapy. Thus, the purpose of this study was to evaluate the feasibility, safety, and efficacy of percutaneous fiducial marker implantation of hepatic malignancies under sonographic guidance for CyberKnife radiation therapy. **Materials and Methods:** From April 2009 to November 2011, we retrospectively reviewed 30 percutaneous fiducial marker implantations in 30 patients with hepatic tumors. All patients underwent percutaneous fiducial marker implantation under sonographic guidance. The feasibility, safety, and efficacy of this technique were analyzed on immediate follow-up unenhanced computed tomography (CT) and 1-week follow-up contrast-enhanced CT. The efficacy of this technique was defined as implantation enabling adequate treatment planning and CT simulation. **Results:** All 30 patients (100%) had successful fiducial marker implantation under sonographic guidance. The mean number of fiducial markers implanted per patient was 4.30 (range: 4-6 seeds). There was one minor complication (3.33%, 1/30). All 30 patients successfully underwent CyberKnife radiation therapy after fiducial marker implantation. **Conclusion:** Sonographic-guided percutaneous fiducial marker implantation of hepatic malignancies is a feasible, safe, and effective technique for preparing patients before CyberKnife radiation therapy.

Key words: Sonographic guidance, CyberKnife radiation therapy, hepatic malignancy



INTRODUCTION

Among the modalities used to treat hepatic malignancies, surgical resection is the only proven curative treatment when primary or metastatic disease is limited to the liver. However, a majority of patients are unable to undergo curative resection because of medical comorbidities and/or severely compromised liver function.^{1,2}

Since 1950s, imaging-guided radiation therapy has been widely used for the treatment of intracranial and spinal tumors.^{3,4} It is the precise application of a high-dose of radiation in a precisely defined target lesion while protecting the surrounding healthy tissue. The CyberKnife radiosurgery

system is a recent, frameless stereotactic system, which allows real-time tracking of tumors during the entire treatment cycle using bony structures (for the skull and upper cervical spine) or implanted fiducial markers (for extracranial sites) as landmarks.^{3,5-9} However, accurate implanting fiducial markers around a tumor is still technical challenge.^{3,5} To the best of our knowledge, limited data regarding the usefulness of sonographic-guided percutaneous fiducial marker implantation for hepatic malignancies.³ Thus, we undertook this study to evaluate the feasibility, safety, and efficacy of percutaneous fiducial marker implantation of liver under sonographic guidance for CyberKnife radiation therapy.

MATERIALS AND METHODS

Patients

From April 2009 to November 2011 (2.5 years), a total of 30 patients with hepatic malignancies were referred for CyberKnife radiation therapy (Accuracy, Inc., Sunnyvale, CA, USA) at a single institution [Table 1]. Percutaneous

Received: July 19, 2014; Revised: March 10, 2015; Accepted: April 08, 2015

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Table 1. Patients' demographics and tumor characteristics

Parameter	Value
Age (years) ^a	62.47±12.72 (37-84)
Sex (male/female)	18/12
Tumor origin (HCC/colorectal carcinoma/ cholangiocarcinoma/breast carcinoma/ angiosarcoma/gastric carcinoma)	16/6/3/3/1/1
Tumor size (cm) ^a	5.47±3.07 (1.6-13.0)
Tumor location (right lobe/left lobe)	16/14

^aData are the mean ± SD, data in the parentheses are the range; SD = Standard deviation; HCC = Hepatocellular carcinoma

fiducial marker implantation under sonographic guidance was performed for them before radiation therapy. All patients met the following criteria for percutaneous fiducial marker implantation: Absence of ascites, a platelet count $\geq 50,000/\text{mm}^3$, and prothrombin activity $\geq 50\%$. The benefits and risks of the procedure were fully explained and a written informed consent was taken. The 30 patients (age range: 37-84 years; mean age: 62.47 years) had the following origin of hepatic malignancies: 16 hepatocellular carcinomas, 6 colorectal carcinomas, 3 cholangiocarcinomas, 3 breast carcinomas, 1 angiosarcoma, and 1 gastric carcinoma. The tumor diameters ranged from 1.6 to 13.0 cm (mean, 5.47 ± 3.07 cm).

Fiducial marker implantation under sonographic guidance

All patients were interviewed before the procedure, and all the fiducial marker implantations were performed by an interventional radiologist with 8 years of experience in sonographic-guided intervention. The patient was placed in supine position. A preliminary unenhanced computed tomography (CT) of the abdomen was obtained to confirm the location of hepatic tumor. The choice of the puncture site for fiducial marker implantation was based on the location of the hepatic tumor and the discretion of the operator. After sterile fashion and administering local anesthetic to the skin at the puncture site, a 19-gauge thin-wall coaxial introducer needle (Temno™; CareFusion, McGaw Park, IL, USA) was advanced into the liver parenchyma with the goal of placing the needle tip near the hepatic tumor under sonographic guidance. The fiducial marker (Radiation Products Design, Inc., Albertville, MN, USA) was then advanced through the needle. Each fiducial marker measured 0.8 mm × 0.5 mm in diameter and length, respectively. Repeat the same procedures at the two to five puncture sites, four to six fiducial markers were placed around the hepatic tumor. Repeat unenhanced CT after the fiducial marker implantation was performed to confirm the locations of fiducial markers and to evaluate the immediate complication.

Definition of technical success of fiducial marker implantation

Technical success was defined as the ability to deposit the fiducial marker close to the tumor with the distance ≤ 5 cm on immediately follow-up unenhanced CT after fiducial marker implantation. Follow-up contrast-enhanced CT of the abdomen was performed 1-week after the fiducial marker implantation to evaluate the fiducial marker migration and delayed complication. Technical efficacy was defined as the ability to deposit the fiducial marker without migration on 1-week follow-up contrast-enhanced CT. To estimate the technical feasibility of fiducial marker implantation, we recorded the number of puncture sites required to place the fiducial markers, the number of fiducial marker per patient, and the time for fiducial marker implantation. To estimate the safety related to fiducial marker implantation, we recorded the immediate complication after fiducial marker implantation on immediately follow-up unenhanced CT and delayed complication on 1-week follow-up contrast-enhanced CT.

Definition of efficacy of fiducial marker implantation

Treatment planning with CT simulation was carried out a minimum of 7 days after fiducial marker implantation to allow for the resolution of tissue inflammation and fiducial marker migration. To assess the efficacy of fiducial marker implantation, we defined satisfactory rate of implantation for CyberKnife treatment as at least four implanted fiducial markers without migration enabled adequate treatment planning and CT simulation.

Statistical analysis

Continuous data were expressed as mean ± standard deviation. Differences between the means of the two groups were analyzed using Student's *t*-test. All *P* values were from two-tailed tests. *P* < 0.05 indicated a statistically significant difference. The analyses were performed using the SPSS software (SPSS 12.0; SPSS, Chicago, Illinois, USA) package for Windows.

RESULTS

Technical feasibility and safety of fiducial marker implantation

Fiducial marker implantation under sonographic guidance was technically successful in all patients [Figure 1]. The distance between fiducial marker and hepatic tumor was ≤ 5 cm on immediately follow-up unenhanced CT. Technical details of fiducial marker implantation are shown in Table 2. Fiducial marker implantation was performed for 16 patients

Sonographic-guided fiducial marker implantation

with tumors located over the right lobe liver and 14 patients with tumors located over the left lobe liver. When classified by tumor location, the average time of implantation procedure of the hepatic tumors located over the right lobe liver was 37.42 ± 11.74 min and 34.63 ± 10.99 min of the tumors located over the left lobe liver, which was not statistically significant difference ($P = 0.60$). The average number of fiducial marker implanted per patient of the hepatic tumors located over the right lobe liver was 4.42 ± 0.67 and 4.25 ± 0.46 of the tumors located over the left lobe liver, which was not statistically significant difference ($P = 0.55$). The average number of puncture site per patient of the hepatic tumors located over the right lobe liver was 3.17 ± 0.83 and 3.25 ± 0.46 of the tumors located over the left lobe liver, which was not statistically significant difference ($P = 0.80$). The technical efficacy of fiducial marker implantation was 98.45% (127/129). Two patients had four and five fiducial markers implantation with one marker migration on 1-week follow-up contrast-enhanced CT [Figure 2]. There were no procedure-related deaths. Only

one patient had small perihepatic hematoma about $3\text{ cm} \times 1\text{ cm}$ in size, in the lateral segment of left lobe liver on immediately follow-up unenhanced CT. The patient had no significant symptom and the perihepatic hematoma was resorbed on 1-week follow-up contrast-enhanced CT.

Technical efficacy of fiducial marker implantation

The satisfactory rate of implantation for CyberKnife treatment was 97.77% (29/30). One patient had four fiducial markers implantation with one marker migration on 1-week follow-up contrast-enhanced CT. All the implanted fiducial markers enabled adequate tracking of the hepatic tumors for patients during all phases of respiration for treatment planning and CT simulation.

Table 2. Technical details and complication of fiducial marker implantation

Parameter	Value
Number of fiducial marker per patient (seed) ^a	4.30±0.59 (4-6)
Number of puncture site per patient ^a	3.20±0.70 (2-5)
Time of implantation procedure (min) ^a	36.30±11.24 (16-60)
Successfully implanted fiducial marker (seed)	129 (100)
Complication (minor)	1 (3.33)
Migration of fiducial marker	2 (1.56)

^aData are the mean ± SD, data in the parentheses are the range or percentage; SD = Standard deviation

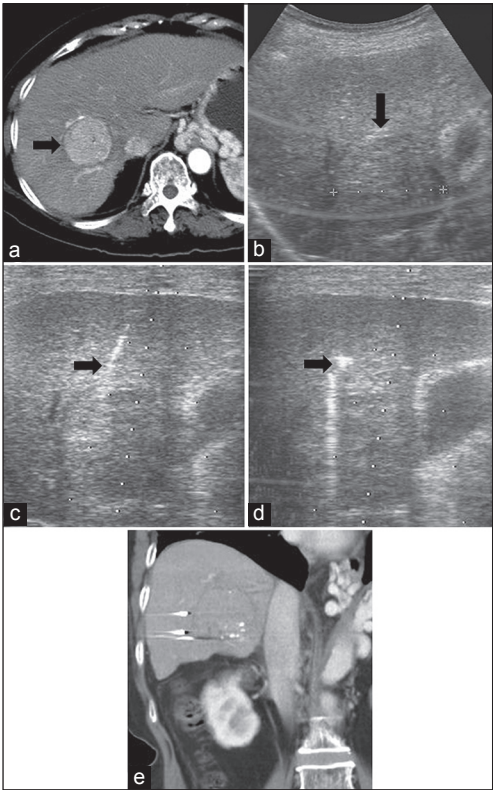


Figure 1. A 69-year-old woman with hepatocellular carcinoma over the segment VIII of liver after sonographic-guided percutaneous fiducial marker implantation. A good enhancing hepatocellular carcinoma over the segment VIII (arrow) on computed tomography (CT) (a), well demonstration of the tumor margin (arrow) on sonography (b), well demonstration of the tip of introducer needle (arrow) under sonographic guidance (c), the fiducial marker implanted (arrow) near the tumor under sonographic guidance (d), fiducial markers located near the tumor in 1-week follow-up contrast-enhanced CT (e)

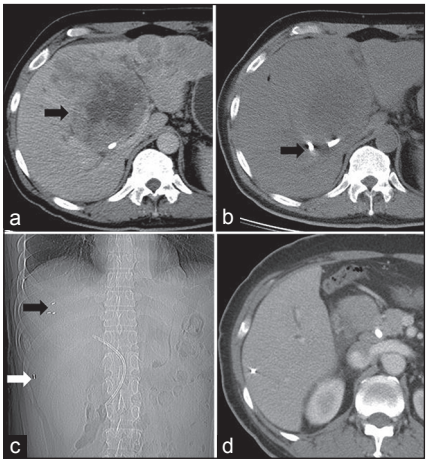


Figure 2. A 50-year-old man with hepatocellular carcinoma over the segment IV and VIII of liver after sonographic-guided percutaneous fiducial marker implantation. A heterogeneous hepatocellular carcinoma over the segment IV and VIII (arrow) on computed tomography (CT) (a), a fiducial marker implanted over the dorsal aspect of tumor (arrow) on immediately follow-up unenhanced CT (b), well demonstration of the implanted fiducial markers on tomography in 1-week follow-up contrast-enhanced CT. Three fiducial markers implanted near the tumor (black arrow) but one fiducial marker migrated to the peripheral zone (white arrow) (c), the migrated fiducial marker over the peripheral zone of segment VI (arrow) in axial contrast-enhanced CT (d)

DISCUSSION

Hepatocellular carcinoma is the most common primary visceral malignancy and hepatic metastases are the most frequency hepatic tumor in the world.^{10,11} Surgical resection is the gold standard treatment when the disease is confined to the liver with the potential for a cure.^{12,13} When operation is not a treatment option, alternative therapies, such as local ablation therapies, transarterial chemoembolization, hepatic arterial infusion chemotherapy, or imaging-guided radiation therapy can play a role in patient management.^{2,3,14} The CyberKnife system is a noninvasive imaging-guided radiosurgery modality that uses orthogonal X-rays to visualize fiducial markers implanted around the tumor for real-time tracking during the entire treatment cycle.¹⁵ The advantage of CyberKnife system is that it can track and compensate for small amounts of respiratory motion, with submillimeter accuracy.¹⁶ Nowadays, the system is widely used for extracranial lesions, such as lesions in liver, pancreas, prostate, kidney, and lung.^{3,5,7,9} Accurate implanting fiducial markers around a target tumor is an important procedure before CyberKnife radiation therapy. The purpose of this study was to evaluate the feasibility, safety, and efficacy of percutaneous fiducial marker implantation of liver under sonographic guidance for CyberKnife radiation therapy.

Regarding the methods for percutaneous fiducial marker implantation of liver, the use of coaxial introducer needle for the insertion into the liver parenchyma under CT guidance seems to be the most popular technique.⁵⁻⁷ However, the tumor margin is not always clearly identified on unenhanced CT, it increases the difficulty and time-consuming of procedure. In this study, we used the 19-gauge coaxial introducer needle for fiducial marker implantation under sonographic guidance. All the procedures of fiducial marker implantation were real-time monitored by sonography and the locations of the fiducial markers were confirmed by the immediately follow-up unenhanced CT. The implantation procedure was usually performed within 40 min. The technical successful rate of fiducial marker implantation was 100% (129/129).

Kothary *et al.*¹⁵ reported that at least three fiducial markers, which do not appear superimposed on orthogonal views are required to give positional information about the tumor for CyberKnife radiation therapy. Kim *et al.*³ also reported that keep a minimum spacing of 20 mm and a minimum 15° angle between the fiducial markers to prevent superimposition on each other are recommended. If the fiducial markers are superimposed on each other in 45° oblique views, the CyberKnife system will interpret them as a single marker. In our study, 4.30 ± 0.59 (range: 4-6 seeds) fiducial markers were implanted per patient and 3.20 ± 0.70 (range: 2-5) puncture sites were selected per patient for fiducial marker implantation.

All the implanted fiducial markers enabled adequate tracking of the target tumor during all phase of respiration for treatment planning and CT simulation. The results of our study showed that at least four fiducial markers and two skin puncture sites per patient were needed for achieving successful CyberKnife radiation therapy.

Some authors have reported that the failure rate of discriminating fiducial marker over the liver seems to increase when we implanted more than three fiducial markers under sonographic guidance because poor spatial accuracy in three-dimension on sonography.³ Some hepatic malignancies, especially of infiltrated hepatocellular carcinoma on cirrhosis are not always visible on sonography, it also increases the difficulty of fiducial marker implantation. In the present study, we used reference landmarks near the target tumor for sonographic guidance when the hepatic tumor was poorly identified by sonography. We also used more than three skin puncture sites when we implanted more than four fiducial markers per patient. All the fiducial markers were successfully implanted near the hepatic tumors with the distance ≤ 5 cm under sonographic guidance on immediately follow-up unenhanced CT.

Fiducial marker migration may degrade the accuracy of tumor tracking during CyberKnife therapy.¹⁷ Migration is most often occurred in fiducial marker implantation in the lung.¹⁵ It may be due to higher incidence of pneumothorax after procedure with poor lung reserve, which results in fiducial markers dropping into the pleural space.¹⁵ In our study, migrations of two markers (1.56%, 2/129) in two patients after implanted fiducial markers in the liver were observed on 1-week follow-up contrast-enhanced CT. The reason of marker migration was possibly from the direct puncture of the hepatic vessels under imaging guidance. To avoid this situation, carefully monitoring the tip of introducer needle away from the hepatic vessels under sonographic guidance and avoid deposition a fiducial marker when the introducer needle is obscured by blood are recommended.

This study has some limitations. First, this was a retrospective study at a single institution where all sonographic-guided procedures were performed by a single experienced radiologist. Second, the overall survival was not included in the outcome measures because the purpose of the present study was to evaluate the benefit of sonographic-guided percutaneous fiducial marker implantation of hepatic malignancies.

CONCLUSION

Sonographic-guided percutaneous fiducial marker implantation of hepatic malignancies is a feasible, safe, and effective technique for CyberKnife radiation therapy.

Sonographic-guided fiducial marker implantation

However, fiducial marker migration was the most common problem in our study; radiologist must pay more attention when performing fiducial marker implantation of liver under sonographic guidance to avoid marker migration.

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