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Original Article

Safety and Efficacy of Percutaneous Fiducial Marker Implantation for Image-guided Radiation Therapy; Initial experience in Ramathibodi Hospital

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Abstract

Purpose: To evaluate the safety and technical success rate of percutaneous fiducial marker implantation in preparation for image-guided radiation therapy.

Materials and Methods: From January 2009 to September 2009, we retrospectively reviewed 21 percutaneous fiducial marker implantations by interventional radiologist in 20 patients. Of the 21 implantations, 3 were in the lung, 9 were in the prostate gland, 8 were in the liver and one was in the pancreas. Procedure-related major and minor complications were documented. Technical success was defined as implantation enabling adequate treatment planning and computed tomographic simulation.

Results: The major and minor complication rates were 4.8% and 19.1%, respectively. Pneumothorax after lung implantation was the most common complication. Pneumothoraces were seen in 2 of the 3 lung implantations (66.6%); a chest tube was required in one of three the lung transplantations. Of the 21 implantations, 17 were successful (80.9%); in 1 implantation at the lung the fiducial markers migrated. However, it not required additional procedures or more implantation.

Conclusions: Percutaneous implantation of fiducial marker at the liver, pancreas and prostate gland is a safe and effective procedure with risks that are similar to those of conventional percutaneous organ biopsy. However, lung implantation is high risk to the pneumothorax that may require chest tube.

Introduction

The advance technology of tumor localization radioation therapy has enabled the use of stereotactic radiation therapy in the treatment of extracranial and extraspinal tumor. The CyberKnife (Accuray, Sunnyvale, California) is one such technology that delivers frameless precision radiation therapy. To track tumor position throughout the respiratory cycle, radiopaque gold markers called "fiducial" markers must be implanted in around the tumor. The fiducial markers act as internal radiological landmarks and move with a constant relationship to the targeted tumor during therapy for the precise delivery of radiation (Figure 1A, 1B & 2). The purpose of this retrospective study was to describe the safety and technical success rate of percutaneous fiducial marker implantation in extracranial locations such as the lung, liver, pancreas and the prostate gland, which performed by interventional radiologist.

Materials and Methods

This retrospective study was granted by the institutional review board. Data were collected from January 2009 to December 2009. 20 patients (mean age, 69.4 years; age range, 49-87 years) underwent 21 procedures

One patient underwent implantations on two separate occasions for anatomically distinct tumors

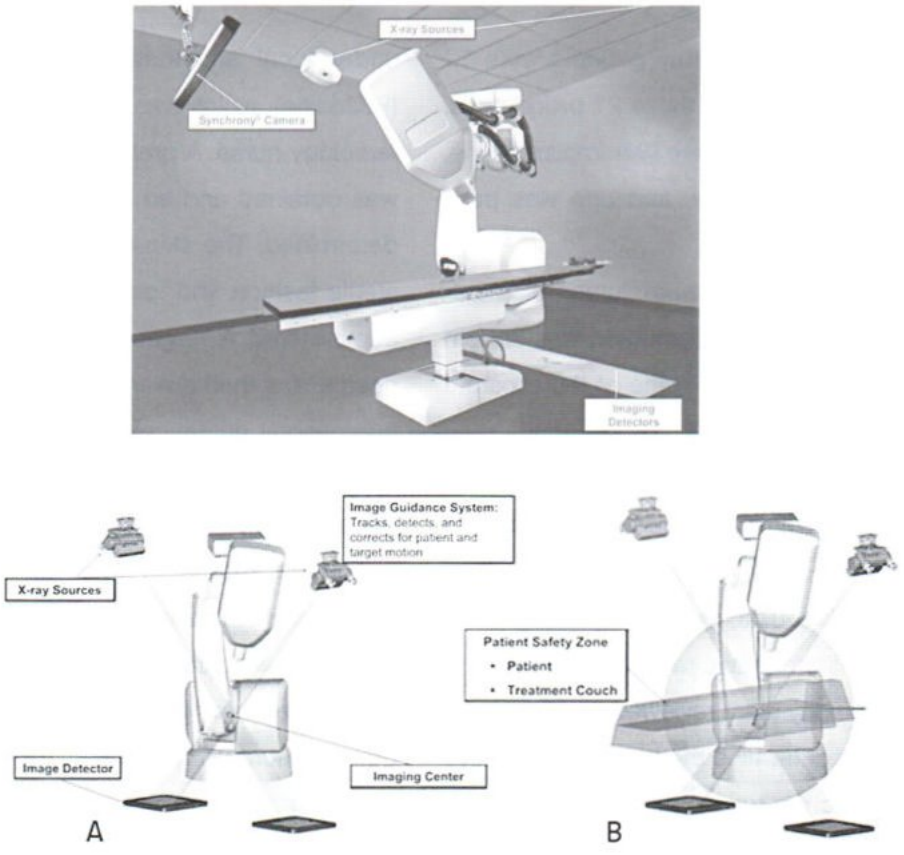

Fig.1 (A&B) CyberKnife and image guidance system

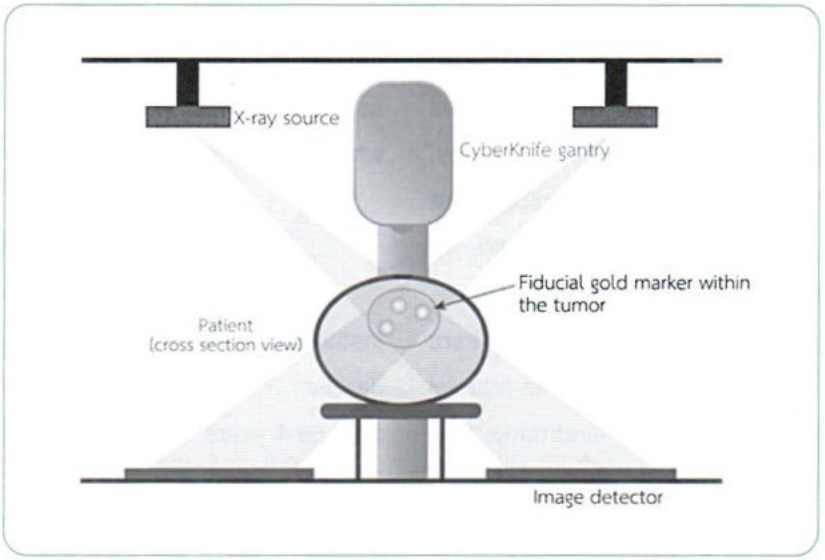

Fig.2 Cross-sectional illustration of the CyberKnife system and demonstrated fiducial gold maker implantation or targeted treatment.

at the liver and pancreas. Twenty patients were 19 men and one was women. Of these 21 procedures, 3 were lung implantations, 8 were liver implantations, 9 were prostatic implantations and one was pancreatic implantation.

The mean overall maximum tumor diameter with exclude the prostatic implantation was 2.9 cm (range 1-5.9 cm). The mean volume of the prostate glands were 67.1 cc (range 24-126 cc).

All cases were discussed at their respective tumor boards and were deemed unresectable or failure for other modality. The patients were then evaluated by the diagnostic radiologist to determine their suitability for stereotactic radiation therapy. The interventional radiology team reviewed the diagnostic imaging studies to determine the best percutaneous needle approach to the tumor. All procedures were performed by using computed tomography (CT) and ultrasound (US) with additional fluoroscopy.

Procedures were performed with the patient under local anesthesia with pain reduced drug (Pethidine), which was administered by a registered radiology nurse. A preliminary unenhanced CT scan was obtained and an appropriate needle trajectory determined. The skin entry site was prepared in a sterile fashion and local anesthesia (lidocaine 1%) administered. A 19-gauge thin-wall coaxial introducer needle was then advanced into the lesion under CT fluoroscopy guidance.

The prostatic implantation was performed under transrectal approach (Figure 7A). A rapid absorbed antibiotic such as ciprofloxacin was administrated in one dose just before and in several doses following the procedure. The cleansing enemas before performing fiducial implantation were also done. Patient on anticoagulatory agents (Aspirin or Warfarin) were no undergo procedure until these drugs had been discontinues. Local anesthesia was used during procedure. This was injected into the neurovascular bundles at base of the prostate gland.

After anesthetic procedure, three to four cylindrical fiducial markers measuring 0.8 mm in diameter and 5 mm in length were deposited via the 19-gauge coaxial introducer needle. The fiducials were introduced into the coaxial needle by using a curved hemostat and advanced into the lesion by using the trochar of the introducer needle.

Because the CyberKnife uses orthogonal x-rays at 45° to vertical to track the tumor and fiducial markers, the markers must be placed in a noncollinear array in different sectors of the tumor to define a three dimensional space enclosing the tumor. Unenhanced CT was performed at the end of procedure to evaluate for immediate complications and confirmed position of these fiducials. In case of implantation with US guidance was performed. The plan radiographic with AP, both obliques (45°) and lateral views was also done for determine the proper position of the fiducial markers.

Patients without any complications were monitored for 12-24 hours and then discharged from the hospital. Patients with complications were admitted for observation and appropriate treatment planning with CT simulation was done a minimum of 7 days after implantation to allow for the resolution of tissue inflammation and fiducial marker migration (Figure 7B &7C).

A custom-made immobilization and proper position of devices were prescribed. The criteria for proper position of the fiducial marker were described as follow (Figure 3 & 4).

1. Minimum 3 fiducial required
2. Minimal distance between fiducial more than 20 mm.
3. Set the minimal angle between three fiducial more than 15 degree for each angles (not colinear placement) (Figure 4).
4. Distance between fiducial marker and target not more than 50-60 mm.

The CT simulation images were transferred to the CyberKnife treatment planning system. The tumor volume and adjacent crucial structures were outlined, and an appropriate radiation dose was prescribed by radiation oncologist.

The fiducial markers were identified on the images, allowing the guidance system to calculate the exact location of the tumor in relation to the fiducial markers and surrounding structures. A treatment plan was formed on the basis of this information, which was then translated to robotic control for the precise delivery of the therapeutic dose.

Complications were documented by using the SIR clinical practice guidelines[1].

A major complication was defined as that requiring therapy with hospitalization for less than 48 hours, major additional therapy, or an unplanned increase in the level of care or hospitalization for more than 48 hours and that causing permanent adverse sequelae or death.

A minor complication was defined as that requiring no or nominal therapy, including overnight hospitalization for observation with no permanent consequence[1].

Technical success was defined as implantation that enabled adequate tracking of the tumor during all phases of respiration for treatment planning and CT simulation. For this, at least three non-collinear fiducials had to be present and adequately visualized on the digitally reconstructed radiographs obtained by the two orthogonal x-ray sources.

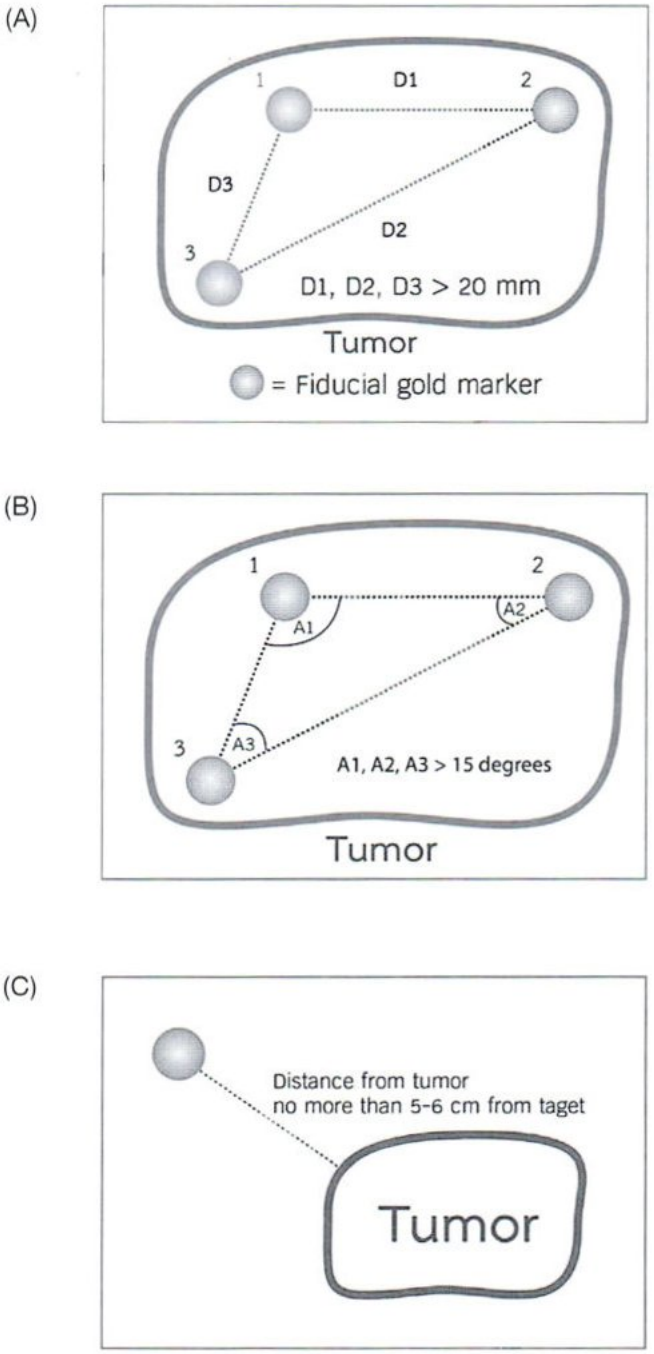

Fig.3 The criteria for proper position of the fiducial marker

A. Minimal distance between fiducial more than 20 mm.

B. Set the minimal angle between three fiducial more than 15 degree for each angles (not colinear placement)

C. Distance between fiducial marker and target not more than 50-60 mm.

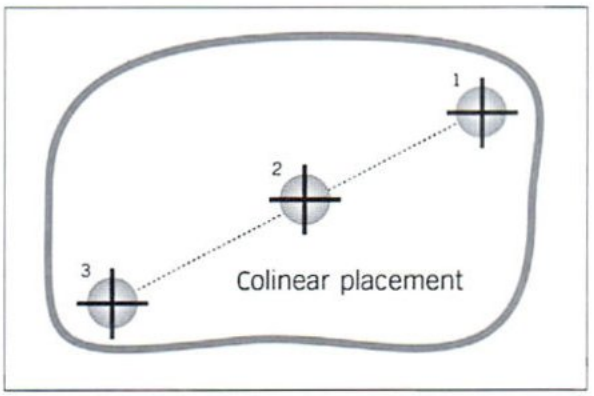

Fig.4 Three fiducial placement with not proper position (Colinear placement)

Results

Safety and Technical Success

The median number of fiducial markers implanted for each tumor was three (range, 2-4). There were no procedure-related deaths. Major complications occurred in one of the 21 implantations (4.76%).

Minor complications occurred in four patients (19.04%). Of the 21 implantations, 17 were technically successful; in one lung implantation (4.76%), the fiducial markers migrated into the pleural space. Three implantations in the prostate gland were too closed than 2 cm in distance, resulting difficult to radiation therapy. The results are summarized in table 1 & 2.

Lung Implantation

A total of three patients underwent lung implantation procedures. Major complications were seen in one of the three lung implantations (33.3%). The most common complications were pneumothorax. One patient (33.3%) was symptomatic and required placement of a chest tube. Localized pulmonary hemorrhage was observed in two patients (Figure 5). Two of three patients had a small amount of hemoptysis. However, none of the patients required additional treatment or transfusion. In one patient (33.3%), the one fiducial marker migrated into the pleural space and cannot ongoing the radiation therapy with cyberknife, which implanted under fluoroscopic guidance (Figure 6).

Liver Implantation

A total of 8 patients underwent liver implantation procedures. There were no major complications. No fiducial marker migration is observed. The entire fiducial markers located in the proper position with criteria as described above.

Pancreas Implantation

One patient underwent two separate procedures for two distinct tumors. He had history of

Table 1 Summary of Patient Demographics

Parameter	Value
Total fiducial marker implantation (n=20)	
Mean patien age	69.4 (49-87)
Sex	
No. of men	19 (95%)
No. of women	1 (5%)
Mean tumor size	2.9 cm (1-5.9)
Lung (n=3)	
Mean tumor size (cm)	3.1 (2.6-3.5)
Liver (n= 8)	
Mean tumor size (cm)	4.1 (2-5.9)
Pancreas (n= 1)	
Tumor size (cm)	4.5
Prostate gland (n=9)	
Mean prostate volume (cc)	67.1 (24-126)

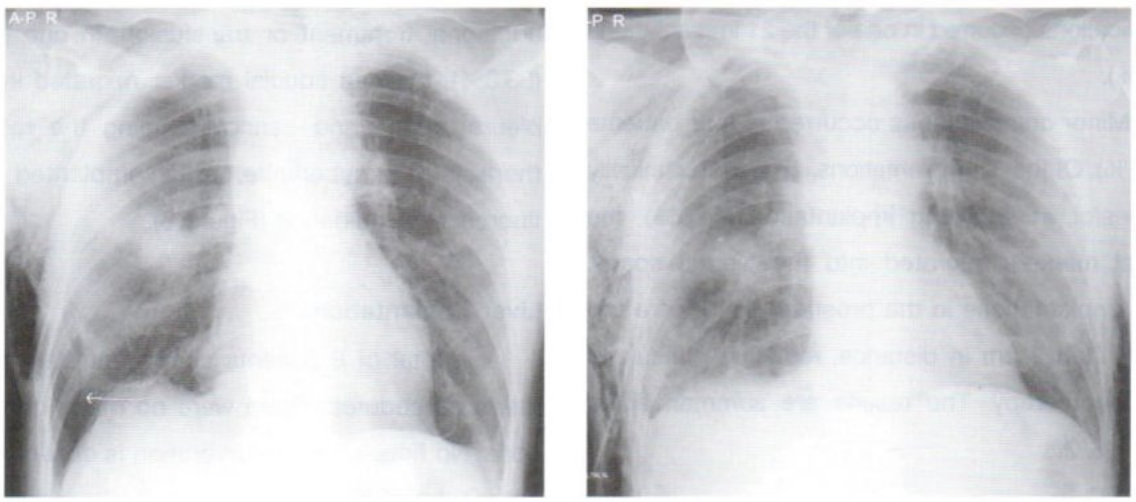

Fig.5 A 66-year-old male with history of recurrent CA lung, presented with severe pneumothorax after fiducial placement. ICD insertion was required for treatment.

Table 2 Summary of Complication and Outcome

Parameter	Value
Total procedure (n = 21)	
Complications	1 (4.8%)
Major	4 (19.1%)
Minor	17 (80.9%)
Technical success	
Lung procedure (n = 3)	
Complications	
Major	
Pneumothorax requiring chest tube	1 (33.3%)
Minor	
Pneumothorax not requiring chest tube	1 (33.3%)
Hemoptysis (not requiring blood transfusion)	3 (100%)
Pulmonary hemorrhage (not requiring blood transfusion)	1 (33.3%)
Technical success	2 (66.7%)
Liver procedure (n = 8)	
Complications	
Major	-
Minor	-
Technical success	8 (100%)
Pancreatic procedure (n = 1)	
Complications	
Major	-
Minor	-
Technical success	1 (100%)
Prostatic procedure (n = 9)	
Complications	
Major	-
Minor (minimal hemorrhage per rectum)	3 (33.3%)
Technical success	6 (66.7%)

colon cancer with liver and pancreatic metastasis. Two separate implantation procedures were performed, using three fiducials for each liver and pancreas. There is no major or minor complication for pancreatic implantation. No migration was detected.

Prostate Implantation

Nine patients with a mean age of 74.9 years (range 67-87 years) participated in this study. Fiducial placement under transrectal guidance was successful in all patients. A total of 34 fiducials were deployed in a four-quadrant manner outlining the prostate

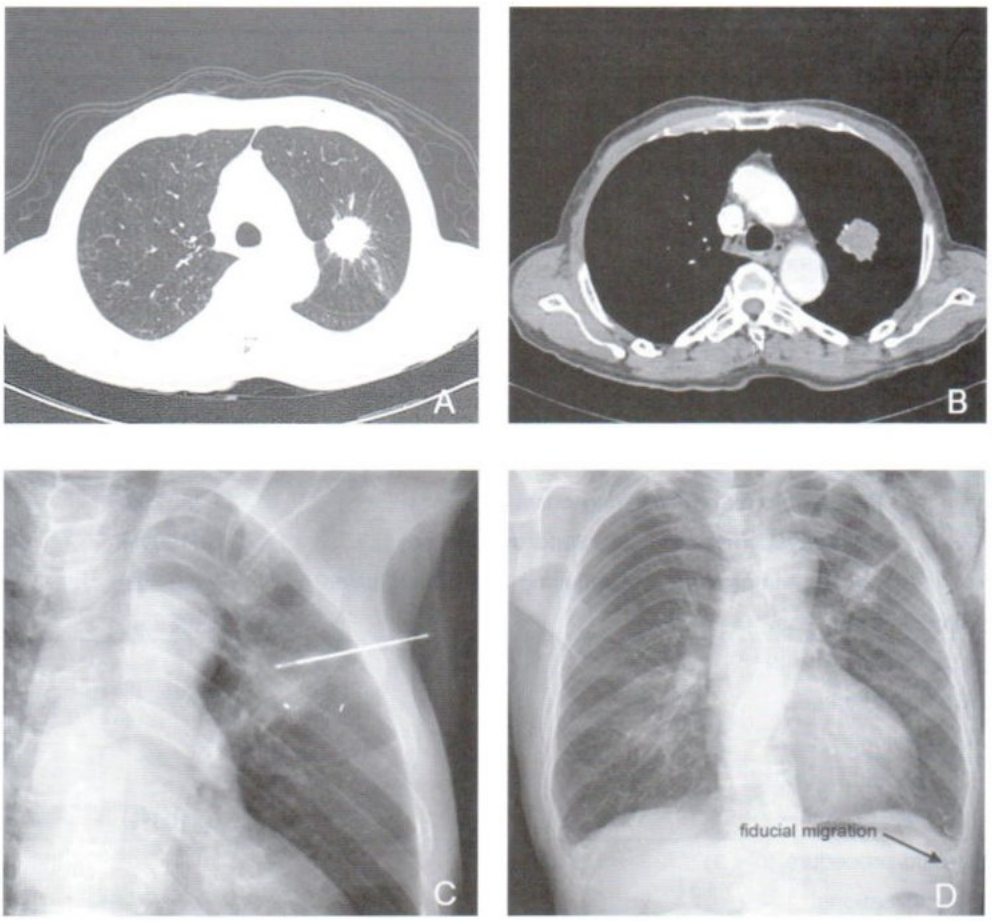

Fig.6 A 78-year-old male, known case of CA lung at LUL, was sent for fiducial placement (A&B). Successful implantation of four fiducial gold markers was performed (C). There was migration of one fiducial into pleural space after 1 week of follow up (D).

gland. There was no evidence of fiducial migration. However, there patients had minimal distance between fiducial less than 20 mm that not appropriate for the radiation therapy.

All patients tolerated the procedure well with minimal discomfort. No major complications occurred during the recovery period at 24 hours after the procedure. Three patients had minimal bleeding per rectum with spontaneous stop after procedures. No evidence of hematuria, dysurea or UTI was observed. There was no reported fiducial migration throughout the course of therapy because this was monitored daily through the comparison of the images acquired on each day of therapy with the initial planning CT.

Discussion

For more than half a century, principles of stereotaxy have been used in radiation therapy. Traditional stereotaxy requires rigid immobilization to establish spatial coordinates for precise guidance.

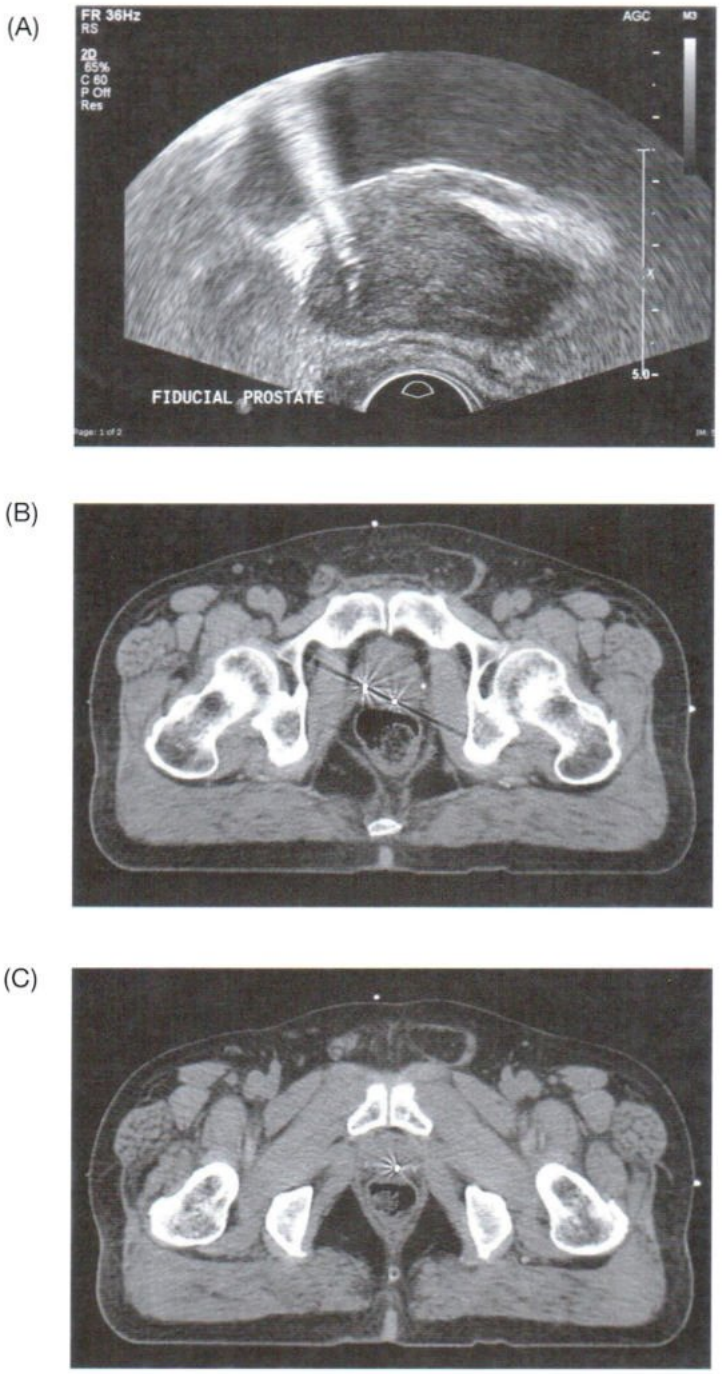

Fig.7 (A) Transrectal US image demonstrates fiducial deployment in the prostate gland. The fiducial marker appears as a hyperechoic, linear structure with an associated hyperechoic shadow. (B&C) Treatment planning with CT simulation was done a minimum of 7 days after implantation.

Table 3 Individual patient characteristic and demographic summary

Case No.	Sex	Age	Underlying/Pathology	Location	Tumor size*	Number of fiducial	Techinique	Major/ Minor complication	Fiducial migration	Fiducial position
1	M	71	CA sigmoid colon with liver & lung metastasis	LUL	2.6	4	CT guidance	-	No	Good
2	M	66	Recurrent CA lung S/P RUL & RML lobectomy	Right hilar region	3.1	3	CT guidance	Pneumothorax with ICD/ Lung hemorrhage	No	Good
3	M	78	Unresected CA lung	LUL	3.5	4	Fluoroscopic guidance	Minimal pneumothorax	Yes	Good for the rest fiducials
4	M	71	HCC	Segment IVa	2.0	4	US guidance	-	No	Good
5	M	76	Recurrent HCC S/P left hepatectomy	Segment VIII	3.7	4	US guidance	-	No	Good
6	M	75	HCC with failure TOCE	Segment II	4.0	3	US guidance	-	No	Good
7	M	56	Metastatic leiomyosarcoma	Segment VII	4.2	3	US guidance	-	No	Good
8	F	60	Liver metatasis	Segment VI	4.4	3	US guidance	-	No	Good
9	M	49	CA colon with liver & pancreatic metastases	Hepatic segment IVa & pancreatic head	4.0 & 5.2	6	US guidance	-	No	Good
10	M	54	HCC S/P TOCE & RFA	Segment VI	5.9	3	US guidance	-	No	Good
11	M	58	HCC S/P TOCE	Segment VII	3.4	3	US guidance	-	No	Good
12	M	82	CA prostate	Prostate gland	4.0x4.2x4.8	4	Transrectal US	-	No	Good
13	M	87	CA prostate	Prostate gland	3.5x4.2x3.9	4	Transrectal US	-	No	Good
14	M	67	CA prostate	Prostate gland	3.8x3.6x3.4	4	Transrectal US	minor localized hemorrhage	No	Good
15	M	76	CA prostate	Prostate gland	3.9x4.2x4.8	4	Transrectal US	-	No	Good
16	M	77	CA prostate	Prostate gland	3.4x1.5x1.8	4	Transrectal US	minor localized hemorrhage	No	Too close
17	M	70	CA prostate	Prostate gland	3x4.5x3.7	3	Transrectal US	-	No	Too close
18	M	72	CA prostate	Prostate gland	2.6x3.9x4.4	3	Transrectal US	-	No	Good
19	M	70	CA prostate with bony metatasis	Prostate gland	3.0x3.2x3.6	4	Transrectal US	-	No	Good
20	M	73	CA prostate	Prostate gland	4.6x3.8x3.6	4	Transrectal US	minor localized hemorrhage	No	Too close

Table 4 Specific Major Complication for Image-guided Percutaneous Biopsy (SIR recommendation)

Major Complications	Reported Rate (%)	Suggested Threshold (%)
Bleeding (requiring transfusion or intervention)		
Large needle (18-gauge or larger)	5-10	10
Small needle (19-gauge or smaller)	3	6
Fine needle (21-gauge or smaller)	0.1-2.0	2
Infection (requiring hospitalization or specific therapy)		
All biposy (sterile)	1	2
Prostatic biopsy (nonsterile)	2.5-3.0	6
Peritonitis (requiring hospitalization or specific therapy)		
Abdominal biopsies	1.5	2
Hemoptysis (requiring hospitalization or specific therapy)		
Lung biopsies	0.5	1
Pneumothorax (requiring chest tube)		
All biopsies (other than lung)	0.5	1
Lung biopsies	5	10

This can be achieved for intracranial and spinal targets with rigid frames but is limited for extracranial sites. The limitations of applying conventional systems to extracranial targets include respiratory and musculoskeletal motion due to patient discomfort. Image-guided radiation therapy systems have been developed that address the task of localization by tracking the target in real time without rigid immobilization.

CyberKnife is one such commercially available system. The CyberKnife combines tracking technology and robotics to offer frameless precision stereotactic radiation therapy. It consists of a lightweight linear accelerator (LINAC) specifically designed for radiation therapy. The second component of this system is real-time image guidance that eliminates the need for external fixation and immobilization. High-resolution digital images are acquired by a pair of orthogonally arranged x-ray radiography systems. The images are electronically registered to the digitally reconstructed radiographs derived from the treatment-planning CT scans. Difference in the anatomic translation and rotation in the three axes are measured by using computer algorithms. The complete process of image acquisition, registration, and compensation is automated and fast enough to provide real-time localization for extracranial applications[2,3]. Respiratory motion, however, is a challenge even for sophisticated robotics such as the CyberKnife. Several previous studies have demonstrated that thoracic and abdominal tumors move by several centimeters

during various phases of the respiratory cycle.

Tumors at the lung base in close proximity to the diaphragm can move up to 25 mm[4]. Pancreatic lesions can move up to 35 mm during respiratory cycles and liver lesions, especially those at the dome, can move similar distances[5]. Respiratory tracking for extracranial applications is essential to ensure that the entire tumor is treated without requiring a substantial increase in the volume of tissue treated. To track the tumor and allow the delivery of radiation throughout the respiratory cycle, a continuous respiratory tracking system called the Synchrony is used along with the standard components of Cyber-Knife for the treatment of thoracic and abdominal lesions.

The fiducial markers act as internal radiologic landmarks, maintaining a fixed relationship with the tumor and with each other. The relative movements of the chest wall and fiducial markers are used to calculate a predictive model that is continuously updated. With the ability to compensate for respiratory motion, stereotactic radiation therapy is rapidly gaining extracranial applications.

Image-guided radiation therapy has also been used in the treatment of primary and secondary liver tumors that are not fully amenable to interventions, such as transarterial chemoembolization and radiofrequency ablation; however, data about image-guided radiation therapy are limited. As the experience with extracranial image-guided radiation therapy grows, a greater number of radiology practices with interventional radiologist will be involved in fiducial marker implantation. Because of interventional radiologist has experience and familiar with technique of image-guided procedure.

In this study, we report our rate of technical success as well as the complication rate for percutaneous fiducial marker implantation.

Few reports exist on this; hence, comparisons are drawn from reported standards for percutaneous biopsies. Our overall major complication rate was 5%, which is within the reported range for percutaneous biopsies[6].

Most complications occurred in patients undergoing fiducial marker placement in a lung tumor. Of the 3 lung implantations, 33.3% developed a pneumothorax that required the placement of a thoracostomy tube. This rate is higher than that reported in the literature (5%) and is above the suggested threshold of 10%[6]. However, other studies that detail complications associated specifically with fiducial marker implantation for thoracic tumors have had pneumothorax and thoracostomy tube insertion rates similar to ours[7]. Previous studies have reported an incidence of pneumothorax as high as 49% in patients with chronic obstructive pulmonary disease after percutaneous biopsy[8]. Because most patients undergoing image-guided radiation therapy are poor surgical candidates due to their underlying poor lung function and general condition, the higher incidence of pneumothorax is not unusual.

Minimal localized pulmonary hemorrhage was seen in 66.6% of the cases; however, none of these patients required any additional therapy such as blood transfusion and the complication rate was well within the suggested SIR threshold (table 4)[6]. Technical challenges in fiducial marker implantation are also responsible for the higher frequency of pneumothoraces and local hemorrhage. For the orthogonal x-ray beams to identify the individual fiducial markers, the fiducial markers must be placed in three or four distinct quadrants. This requires manipulation of the needle within the lung parenchyma, which, in theory, could increase the risk of

local hemorrhage. Migration of the fiducial maker into the pleural space was observed in one patient who implanted under fluoroscopic guidance. Therefore one fiducial was implanted near the pleural space and consequence migration of the fiducial was observed in 7 days later. However, the radiation therapy planning was still processed because three fiducial markers with appropriated position were placed.

External skin markers and bony landmarks were traditionally used as surrogates for prostate position during the radiotherapeutic management of prostate cancer. It has been shown that the treatment margins used to compensate for daily organ motion and setup uncertainties could be as large as 1.5-2 cm if these surrogates were used[9]. These large margins are not compatible with the delivery of high radiation doses above 70 Gy that are used in current routine practice.

During recent years, imaging and localized techniques prior to and during the daily treatment delivery have allowed better localization of the prostate and tighter margins[10]. Implantation of fiducial markers into the prostate gland with image-based radiographic methods is technique that is increasingly being used for targeting. In this study, there were only minor complications with minimal bleeding per rectum in three patients (33.3%). No other complication was observed. To our knowledge, there was only one study in the literature reporting in detail marker-induced toxicity in a large patient group. In that study, Langenhuijsen et al[11] reported their experience with fiducial markers in 209 patients. After transrectal implantation of four gold markers, the side effects in a mean time of 90 weeks were recorded. Haematuria lasting 3 days and rectal bleeding occurred in 3.8% and 9.1% of the patients, respectively.

Compared with diagnostic biopsy data, where multiple biopsy cores are taken, our complication rates seem to be acceptable. Two large European screening programs noted haematuria in 23-63% of men after biopsy, rectal bleeding in 2.1-21.7% and urinary tract infection in 3.5-10.9%[12,13].

There of nine patients had minimal distance between fiducial less than 20 mm that too close for discriminated length of CyberKnife therapy. In our experience, the fiducial plantation of the prostate gland under transrectal US guidance had limited angles and filed of view of implanted needles.

We could not demonstrate any detrimental effects of advanced tumor stage or shorter duration of hormonal treatment on bleeding complications, as shown by Langenhuijsen et al[11]. A possible explanation could be that our longer median time on hormonal treatment (12 weeks VS 7 weeks) at the time of implantation allowed maximal shrinkage in tumor volume and decreased vascularization.

Our study had only one case for pancreatic implantation without major or minor complication. Alternate approaches such as endoscopic ultrasonography have been successful for certain abdominal and thoracic tumors[14] that are difficult or unsafe targets for a percutaneous approach and should be considered for any tumor adjacent to a hollow viscus.

Overall, technical success was high, with successful four-quadrant fiducial marker implantation in 80.9% of cases. Fiducial marker migration has been evaluated in the lungs as well as in abdominal and prostatic tumors[15,16]; however, most of these reports have used other modalities of implantation, such as bronchoscopic or endoscopic placement. Irrespective of that, fiducial marker migration or

"settling" is a known phenomenon and can occur up to 7 days after implantation. Hence, most centers advocate waiting at least 7 days after implantation before performing CyberKnife planning CT. In our study, substantial migrations were seen predominantly in the lungs (33.3%). This migration may be related to the incidence of pneumothorax.

Given this, alternate fiducial marker agents (eg. platinum coils) or alternate modalities (eg. bronchoscopic implantation)[17] should be further evaluated to revolve this problem.

In conclusion, the percutaneous implantation of fiducial markers can be achieved with a relatively low rate of major complications and high technical successful rate in liver and prostate implantation. However, fiducial marker migration and major complication (severe pneumothorax) may occur in lung implantations. This may necessitate additional procedures or the implantation of alternate agents (eg. coils) or bronchoscopic or endoscopic placement.

Limitations of this study include the small number of patients and single-center experience, particularly in the pancreatic and lung implantations.

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