Original Article

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# Safety and Efficacy of Ultrasound-Guided Fiducial Marker Implantation for CyberKnife Radiation Therapy

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**Objective:** To evaluate the safety and technical success rate of an ultrasound-guided fiducial marker implantation in preparation for CyberKnife radiation therapy.

**Materials and Methods:** We retrospectively reviewed 270 percutaneous ultrasound-guided fiducial marker implantations in 77 patients, which were performed from June 2008 through March 2011. Of 270 implantations, 104 were implanted in metastatic lymph nodes, 96 were in the liver, 39 were in the pancreas, and 31 were in the prostate. During and after the implantation, major and minor procedure-related complications were documented. We defined technical success as the implantation enabling adequate treatment planning and CT simulation.

**Results:** The major and minor complication rates were 1% and 21%, respectively. One patient who had an implantation in the liver suffered severe abdominal pain, biloma, and pleural effusion, which were considered as major complication. Abdominal pain was the most common complication in 11 patients (14%). Among nine patients who had markers inserted in the prostate, one had transient hematuria for less than 24 hours, and the other experienced transient voiding difficulty. Of the 270 implantations, 261 were successful (97%). The reasons for unsuccessful implantations included migration of fiducial markers (five implantations, 2%) and failure to discriminate the fiducial markers (three implantations, 1%). Among the unsuccessful implantation cases, six patients required additional procedures (8%).

**Conclusion:** The symptomatic complications following ultrasound-guided percutaneous implantation of fiducial markers are relatively low. However, careful consideration of the relatively higher rate of migration and discrimination failure is needed when performing ultrasound-guided percutaneous implantations of fiducial markers.

**Index terms:** *Fiducial marker; Radiation oncology; Ultrasonography; interventional; Imaging-guided radiation therapy*

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## INTRODUCTION

The CyberKnife system is a non invasive image-guided frameless robotic radiosurgery modality considered to be an alternative to conventional surgery for the treatment of both cancerous and non-cancerous tumors (1). Nowadays, the system is widely used for extracranial lesions, such as lesions in intra-abdominal organs or lung lesions. As the lesions are movable on respiration, they are tracked by the circumstantial insertion of fiducial markers, which also

helps plan the CyberKnife treatment. According to previous studies by Sotiropoulou et al. (2) and Kothary et al. (3), fiducials have usually been placed under CT-guidance. Due to the safety and efficacy of fiducial implantation have also been reported to be placed under CT-guidance only. However, trans-abdominal or trans-rectal ultrasound-guided fiducial marker implantation has been performed for intraperitoneal or pelvic tumors. We also evaluated the placement of fiducial markers under US-guidance with respect to safety and technical success rate in the preparation for CyberKnife radiation therapy.

## MATERIALS AND METHODS

### Patients

Our institutional review board approved this retrospective study. From June 2008 to Mar 2011, 77 consecutive patients (Men: 45, Women: 32, mean age: 60 years old, range: 36-79) who had undergone percutaneous ultrasound-guided fiducial marker implantations for CyberKnife therapy (Accuray, Inc., Sunnyvale, CA, USA) of the intra-abdominal organs were enrolled in this study. All the patients elected to undergo CyberKnife radiation therapy after having a discussion with a radiologist, radiation oncologist, and oncologist. We implanted 270 fiducial markers into 77 patients (number of fiducials: two to six fiducial implantations/patient mean: 3.4 in the prostate, 3.5 in other sites including). Among the 270 implantations, 104 were inserted in the metastatic lymph nodes (32 patients), 96 were inserted in the liver (24 patients), 39 were inserted in the pancreas (12 patients), and 31 were inserted in the prostate (nine patients). The mean size of the target tumor had a maximum diameter of 3.3 cm.

Two-hundred twenty-two fiducial markers in 64 patients were inserted via the trans-abdominal route whereas 48 fiducial markers in 13 patients were inserted via the trans-rectal route. 31 fiducial markers in the prostate glands of nine patients, and 17 fiducial markers in the metastatic lymph nodes in the pelvic cavity of four patients were implanted under trans-rectal ultrasound guidance (Table 1).

**Table 1. Summary of Patient Demographics**

| Parameter | Value | No. of Fiducial Markers |
|---|---|---|
| Total patient | 77 | 270 |
| Men | 45 | |
| Women | 32 | |
| Mean age (yr) | 60 (range; 36-79) | |
| Mean tumor size (cm) | 3.33 | |
| Liver (Trans-abdominal USG) | 24 | 96 |
| HCC | 8 | 32 |
| Cholangiocarcinoma | 3 | 11 |
| Pancreas ca. metastases | 4 | 13 |
| Colon ca. metastases | 4 | 19 |
| GB ca. metastases | 2 | 8 |
| Breast ca. metastases | 2 | 9 |
| Stomach ca. metastases | 1 | 4 |
| Metastatic lymph node | 32 | 104 |
| Trans-abdominal USG | 27 | 87 |
| Stomach ca. metastases | 5 | 17 |
| HCC metastases | 4 | 12 |
| Ovarian ca. metastases | 4 | 13 |
| Colon ca. metastases | 3 | 10 |
| Pancreatic ca. metastases | 3 | 10 |
| GB ca. metastases | 3 | 10 |
| Others | 5 | 15 |
| Trans-rectal USG | 5 | 17 |
| Colon ca. metastases | 3 | 11 |
| Ovarian ca. metastases | 2 | 6 |
| Pancreas (Trans-abdominal USG) | 12 | 39 |
| Adenocarcinoma | 10 | 32 |
| IPMN | 1 | 3 |
| Islet cell tumor | 1 | 4 |
| Prostate gland (Trans-rectal USG) | 31 | 9 |

### Fiducial Marker Implantation

All the fiducial marker implantations were performed by a gastrointestinal radiologist with 13 years of experience. By reviewing the previous diagnostic imaging studies for methods such as computed tomography, the best percutaneous needle approach was planned and fiducial insertion was performed under ultrasonographic guidance (IU 22, Philips, Einthoven, Netherlands) with a convex probe (2-5 MHz) at transabdominal ultrasonography and an endorectal probe (5-9 MHz) at transrectal ultrasonography. A free-hand style was used for the transabdominal ultrasonography, and needle guidance was used for the transrectal ultrasonography.

The skin entry site, which was kept sterile following disinfection with betadin, was prepared, and local anesthesia (lidocaine 1%, 10 mL) was administered. Under

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Ultrasound (US)-guidance the radiologist placed two to six gold pins (A fiducial marker kit, Civco, Maarn, the Netherlands) on and around the target, using 18-gauge introducer needles. Each fiducial marker measured 0.9 x 3.0 mm in diameter and length, respectively. When performing the fiducial implantation, it is advised to keep a minimum of 20 mm spacing, and a minimum 15° angle between the fiducials. Moreover, the fiducials should not be more than 50 to 60 mm away from the target.

This implantation procedure was usually performed within 20 minutes. Two or three days after the implantation, a CyberKnife therapy planning radiograph was performed, followed by a CyberKnife planning CT for the simulation of radiation treatment in all the patients within a span of two weeks. CT was performed using a 4-slice MDCT scanner (Sensation 4, Siemens Medical System, Forchhein, Germany). The imaging parameters included a 4.0 x 2.5 mm section detector collimation, 120 kV, 145 mAs, 15 mm per second table speed, pitch of 6, and a 1 mm reconstruction interval.

### Analysis

Upon review of the medical records CyberKnife therapy planning radiographs and the planning CT for the evaluation of procedure-related complications were performed. During and after the implantation, the major and minor procedure-related complications were documented. We only recorded the immediate complications until the time of the CyberKnife planning CT (within 2 weeks).

The major/minor complications were divided by the outcome and according to the SIR Classification System for Complications. Minor complications were divided into two types (A. No therapy and of no consequence, B. Nominal therapy and of no consequence; includes overnight admission for observation only). Major complications were divided into four types (C. Required therapy and minor hospitalization (< 48 hours), D. Required major therapy and an unplanned increase in the level of care, prolonged hospitalization (> 48 hours), E. Permanent adverse sequelae, F. Death).

Also, research about whether the fiducial implantation was successful or not was carried out, and we reviewed the CyberKnife therapy planning radiographs and planning CT images. We defined technical success as the implantation enabled adequate treatment planning and CT simulation. The cases in which more than two fiducial markers overlapped, or reimplantation was needed due to an unexpected occurrence such as fiducial migration, were considered as technical failure.

## RESULTS

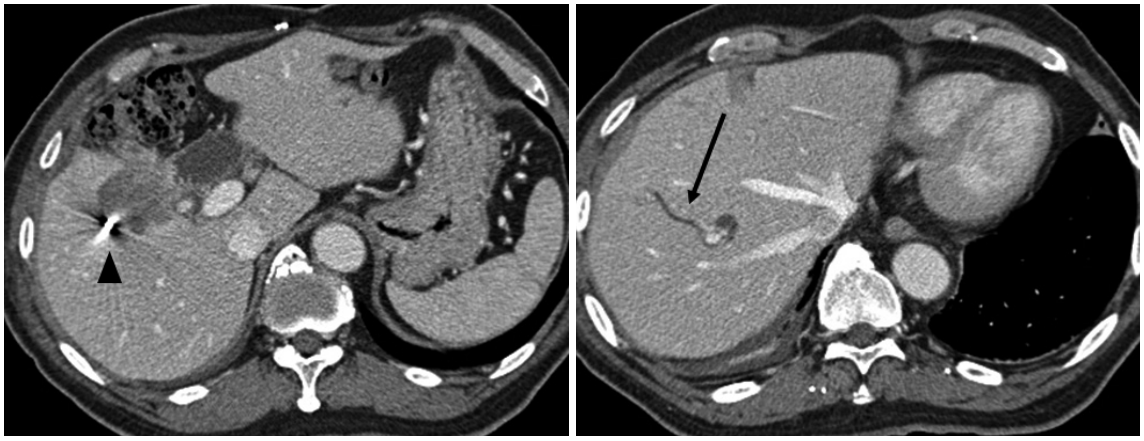
### Immediate Complication

When conducting 270 fiducial implantations in 77 patients, there was one patient with major complication (1.3%) and 16 patients with minor complications (20.8%) (Table 2).

The patient with a major complication had previously undergone Whipple's operation due to CBD cancer. A newly-appeared, 3.7-cm, low-density mass in segment V of the liver on the follow up CT scan (this was presumed to be metastasis) was found. The patient was implanted with four fiducial markers under trans-abdominal ultrasound-guidance for the planning of CyberKnife therapy. Following the implantation, the patient complained of local pain in the insertion site. Analgesics and conservative treatment were performed; however, after 11 hours from the time of fiducial marker insertion, the patient's body temperature rose to 38.6°C and dyspnea as well as right flank pain developed. The patient's pleural effusion gradually increased

**Table 2. Immediate Complications of Ultrasound-Guided Fiducial Marker Implantation**

| Complication | No. of Patients (%) |
|---|---|
| Trans-abdominal USG-guided | 63 (100) |
| No complications | 51 (81.0) |
| Major complications | 1 (1.6) |
| Minor complications | 11 (17.4) |
| Abdominal pain-no analgesics | 4 (6.3) |
| Abdominal pain-analgesics | 5 (7.9) |
| Fever | 1 (1.6) |
| Skin bullae | 1 (1.6) |
| Trans-rectal USG-guided | 14 (100) |
| No complications | 9 (64.3) |
| Major complications | 0 (0) |
| Minor complications | 5 (35.7) |
| Fever | 1 (7.1) |
| Pain | 2 (14.3) |
| Transient voiding difficulty | 1 (7.1) |
| Transient hematuria | 1 (7.1) |
| Total | 77 (100) |
| No complications | 60 (77.9) |
| Major complications | 1 (1.3) |
| Minor complications | 16 (20.8) |



A B

**Fig. 1. Major complications.**
61 year-old-man with hepatic metastasis from recurrent comon bile duct cancer underwent successful implantation of fiducial markers around tumor. After procedure, patient complained of fever, dyspnea and right flank pain. CT **(A)** shows well-located fiducial marker (arrowhead) around hepatic metastatic tumor and more upper level CT **(B)** shows ductal dilatation (arrow) of peripheral intrahepatic bile duct. Also, note pleural effusion and subcapsular hematoma around portion of liver dome (not seen).

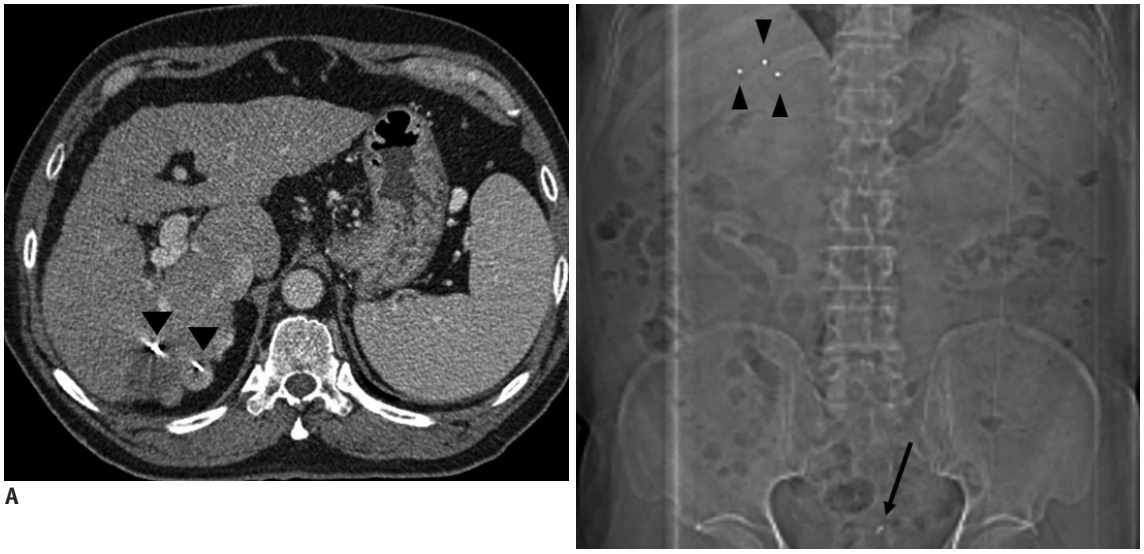


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**Fig. 2. Fiducial migration.**
59 year-old-man with HCC in liver had undergone implantation of 4 fiducial makers around tumor. Two weeks later, only 3 fiducial markers (arrowheads) were found around HCC on CyberKnife planning CT scan **(A)** and missing fiducial marker (arrow) was found in pelvic cavity on scanogram **(B)**.

during the five days after the procedure. Following this, percutaneous-catheter insertion was performed for the pleural effusion. The patient's condition gradually improved after percutaneous-catheter insertion. The CyberKnife planning CT was taken two weeks after fiducial implantation and the CT scan showed a newly appeared subcapsular fluid collection around the liver and biliary dilatation of the peripheral intrahepatic duct, which was suspected to be a biloma. However, the patient did not complain about further symptoms. The patient suffered from a few complications, yet the four fiducial markers were well located in the target tumor. It could be seen on the follow-up CT that the tumor decreased in size from about 3.7 cm to 2.0 cm at one month after the CyberKnife treatment (Fig. 1).

Sixteen patients (20.8%) had minor complications that only required overnight admission for observation and no or minimal therapy. Eleven patients had abdominal pain, four of which did not require specific treatment during the follow-up period. Moreover, two patients had mild fever that also did not require any follow-up treatment, and

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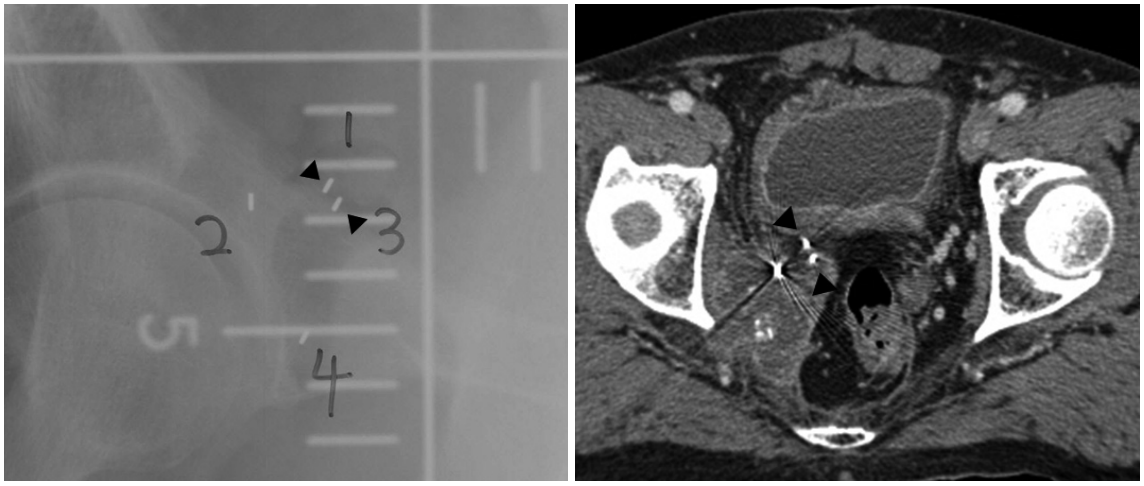


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**Fig. 3. Failure of fiducial discrimination.**
55 year-old-man had metastatic lymph node from rectal cancer in right pelvic cavity. We implanted 4 fiducial markers within lesion by trans-rectal ultrasound-guidance. Two of markers (between number 1 and number 3, arrowheads) overlapped on CyberKnife planning radiograph **(A)**, while two overlapped fiducial markers (arrowheads) are also seen on CyberKnife planning CT scan **(B)**.

**Table 3. Technical Success Rate of Ultrasound-Guided Fiducial Marker Implantation**

| Technical Aspect | No. of Patients (%) | No. of Fiducials (%) |
|---|---|---|
| Trans-abdominal USG guided | 63 | 222 |
| Successfully implanted fiducials | 56 (88.9) | 215 (96.8) |
| Technical failure | 7 (11.1) | 7 (3.2) |
| Migrated fiducials | 5 (7.9) | 5 (2.3) |
| Discrimination failed fiducials | 2 (3.2) | 2 (0.9) |
| Trans-rectal USG-guided | 14 | 48 |
| Successfully implanted fiducials | 12 (85.7) | 46 (95.8) |
| Technical failure | 2 (14.3) | 2 (4.2) |
| Migrated fiducials | 1 (7.1) | 1 (2.1) |
| Discrimination failed fiducials | 1 (7.1) | 1 (2.1) |
| Total | | |
| Successfully implanted fiducials | 68 (88.3) | 261 (96.7) |
| Technical failure | 9 (11.7) | 9 (3.3) |
| Migrated fiducials | 6 (7.8) | 6 (2.2) |
| Discrimination failed fiducials | 3 (3.9) | 3 (1.1) |

one patient had mild transient bullae change at the skin puncture site and did not require specific treatment other than a simple dressing. Lastly, there were two patients with nonspecific urinary symptoms.

As guides for transrectal ultrasound, fiducial markers were inserted into fourteen patients. Among them, nine patients' fiducial markers were inserted to the prostate gland, and the other five into the metastatic lymph nodes in the pelvic cavity. When these implantations were conducted, one patient had transient hematuria that did not last for more than a day and it did not require any specific treatment. Another patient had transient voiding difficulty that required nelaton catheter voiding. None of the patients had major complications that required long-term hospitalization.

### Technical Aspect

Of the 270 fiducial implantations, 261 (96.7%) were considered to be successful. However, the migration of fiducial markers was observed for six implantations (2.2%) in six patients. In the case of the planning CT scanning for the actual treatment, since the treatment is not feasible when fiducial markers migrate more than 6 cm from the target, the procedure needs to be re-done, which was considered a technical failure in this study. Of the six failed implantations, five were implanted for intraabdominal metastatic lymph nodes and one of them was implanted for hepatocellular carcinoma (Fig. 2).

We also observed a failure to discriminate fiducial markers for three implantations (1.1%). Each was implanted for an intra-abdominal metastatic lymph node (Fig. 3), cholangiocarcinoma and pancreatic body cancer, respectively. Among total 77 patients, six patients (7.8%) required additional procedures for reimplantation of fiducial

markers, and one of them was reimplanted under a CT-guidance (Table 3).

## DISCUSSION

Stereotactic radiosurgery was primarily developed in Sweden in the 1950s (4). Radiosurgery is the precise application of a high dose of radiation in a precisely defined target volume while protecting the surrounding healthy tissue. In the beginning, this method was only used for brain lesions. Stereotactic radiosurgery previously utilized a stereotactic body frame to compensate for respiratory motion. This was uncomfortable to patients because treatment involved a long immobilization period (5).

The CyberKnife system is a recent, frameless stereotactic radiosurgery system which allows real-time tracking of tumors during the entire treatment cycle through the synchrony system. This system uses a combination of internal fiducial markers around the target tumor and light emitting optical diodes. It can predict the internal tumor location by coupling the motion of the light emitting optical diodes and the internal fiducial markers. It also adjusts for respiratory variations in real-time. The real-time imaging tracking of the CyberKnife system allows patient movements to be tracked with a spatial accuracy of 1 mm (1, 6).

Implanting internal fiducial markers into or around a tumor is an important procedure for image-guided radiotherapy, such as CyberKnife therapy. Three to six markers are recommended to be implanted. A fiducial marker is less than 2.0 mm in diameter and is a spherical internal radiologic land marker. For bio-compatibility and good contrast on X-ray images, the marker is made out of gold (99.99% purity) (1, 6-9).

The marker is introduced percutaneously via an 18-gauge introducer needle. Usually, the marker implantation is guided by a CT scan (2, 3), but is occasionally guided by trans-abdominal or trans-rectal ultrasound for intra-abdominal lesions. Ultrasound provides real-time monitoring of the whole procedure and more comfortable handling during an intra-abdominal procedure. Therefore, we thought ultrasound-guided implantation could raise the success rate over currently used methods. Ultrasound can also reduce radiation hazard compared to a CT-guided procedure.

When performing a fiducial implantation, it is advised to keep a minimum spacing of 20 mm and a minimum 15° angle between the fiducials. Moreover, the fiducials should not be more than 50-60 mm away from the targets (10, 11), if the markers are superimposed on each other in the 45° oblique views, the Cyber Knife system will interpret them as a single marker (12). Therefore, the implantation should be executed with consideration of all these circumstances.

As for the results, the overall major complication rate was 1.3% and the minor complication rate was 20.8%. The major complication rate was generally comparable to the previously reported complication rate (2.0%) of the image-guided percutaneous biopsy (13), whereas any major complication by trans-rectal ultrasound-guided implantation was not witnessed. A minor complication was defined as a complication that had no negative impact on a particular treatment. That is, the complications associated with ultrasound-guided fiducial marker implantations were not regarded as dangerous compared to other types of biopsies. Also, the major complication rate was lower than that of the previously reported CT-guided fiducial marker implantation study by Kothary et al. (3), which found a 5% complication rate (7 out of 139 implantations).

For the evaluation of technical success, the study demonstrated the migration of six fiducial markers (2.2%) in six patients, as well as three cases of implantation (1.1%) that failed to allow discriminating fiducial marker. As a result, the successful implantation rate was 96.1%. This was similar to the previously reported success rate of CT-guided implantation (95.7%) (3). The reason for the high rate of migrations was possibly from the movement of the mesentery (five implantations). Another case of migration involved a small hepatocellular tumor located at the adjacent hepatic capsule.

Overall, 7.8% (six patients) of all the patients required additional implantations of fiducial markers. While there have not been any previous reports on the reimplantation rate, the above figure implies that a repeated procedure for a relatively high number of patients was needed for comparison to the complication rate. Three out of these six patients had been treated for intra-abdominal lymph node metastases: two for liver implantation and the other for pancreas implantation.

Additionally, as ultrasound lacks spatial accuracy in three-dimensions compared to CT scans, the chances of failing to discriminate fiducial markers seems relatively high. The risk of discrimination failure seemed to increase when we implanted more than three fiducial markers. Hence, we should be more cautious when implanting the 3rd and 4th fiducial markers.

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Our study had several limitations. First, it was a retrospective review from a single institution. Thus, it could include a selection and interpretation bias. There were a relatively large number of patients with metastatic lymph nodes compared with the number of patients with a primary tumor. Our institution is a tertiary center where end stage patients and recurrent patients are transferred from other hospitals. The large number of patients with metastatic lymph nodes could have influenced the results of the technical success rate due to the increased rate of mesenteric implantation. However, most CyberKnife treatment is practiced at a tertiary center. So, the overall patient demographics could be similar to ours.

Second, we only included immediate complications from the time of planning the CyberKnife CT until two weeks after the fiducial marker implantation . We did not record long term complications beyond two weeks after CyberKnife therapy. We believed that any longer term complications were not remarkably associated with the US-guided procedure.

The growing number of CyberKnife treatments has recently expanded the role of radiologists who conduct fiducial marker implantations. While studies on the CT-guided practices can be found, the safety of US-guided implantation and its technical success rate have not been previously reported.

Ultrasound-guided fiducial marker implantation is a safe surgical operation that shows a similar complication rate, as well as high technical success rate to that of the CT-guided practice or biopsy. Nonetheless, as we had a high reimplantation rate; radiologists must pay careful attention when performing ultrasound-guided fiducial marker implantations.

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