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**Percutaneous insertion of hepatic fiducial true-spherical markers for
real-time adaptive radiotherapy**

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Percutaneous insertion of hepatic fiducial true-spherical markers for real-time adaptive radiotherapy

Purpose: This study evaluated the success rate and complications of percutaneous implantation of hepatic fiducial true-spherical gold markers for real-time adaptive radiotherapy (RAR), which constitutes real-time image-guided radiotherapy with gating.

Materials and Methods: We retrospectively evaluated 100 patients who underwent 116 percutaneous intrahepatic implantations of 2-mm-diameter, spherical, gold fiducial markers before RAR from 1999 to 2016, using Seldinger's method. We defined technical success as marker placement at intended liver parenchyma, without mispositioning, and clinical success as successful tracking of the gold marker and completion of planned RAR. Complications related to marker placement were assessed.

Results: The technical success rate for true-spherical gold marker implantation was 92.2% (107/116). Nine of 116 markers migrated (intraprocedurally in 7 patients, delayed in 2 patients). Migration out of the liver ($n = 4$) or intrahepatic vessels ($n = 5$) occurred without complications; these markers were not retrieved. The clinical success rate was 100.0% (115/115). Abdominal pain occurred in 16 patients, fever and hemorrhage in 7

patients each, and pneumothorax and nausea in 1 patient each. No major complications were encountered.

Conclusions: Percutaneous transhepatic implantation of true-spherical gold markers for RAR is feasible and can be conducted with a high success rate and low complication rate.

KEY WORDS: fiducial marker, percutaneous transhepatic implantation, radiation therapy, true-spherical marker

Introduction

Highly focused external-beam radiation therapy, such as stereotactic ablative radiotherapy, has been reported as an effective alternative to radical surgery for hepatic malignant tumors [1]. Because its success greatly depends on the accuracy of daily set-up of the patient, as well as the management of respiratory tumor motion, image-guided radiation therapy (IGRT) using imaging equipment in the treatment room is expected to further improve the clinical results. Daily set-up of the patient has been shown to be improved by IGRT using on-line X-ray cone beam computed tomography (CBCT), deformable registration software, four-dimensional reconstruction of CBCT, and on-line magnetic resonance imaging (MRI) [2, 3, 4]. For the management of respiratory tumor

motion during irradiation, real-time adaptive radiotherapy (RAR) is expected to reduce uncertainty [5]. RAR is defined as radiotherapy that, throughout therapeutic irradiation, monitors patient anatomy or physiology; based upon that information, RAR allows autonomous adjustments of treatment parameters during therapeutic irradiation without operator intervention [5]. In an RAR system in the clinic, internal motion within tumors can be automatically tracked 30 times per second by 2 sets of fluoroscopy images with real-time pattern recognition of implanted fiducial markers; the therapeutic beam is controlled to irradiate/not to irradiate the patient with 0.05-second intervals for gating [6, 7]. Recently, an advanced proton RAR system has also been developed for use in treatment of large hepatic tumors [8].

As a surrogate marker for hepatic tumors, the fiducial marker is required to be implanted as close as possible to the tumor [9]. There have been several reports regarding the transarterial hepatic implantation of an embolization coil [10] and percutaneous transhepatic implantation of a gold marker [11-17]. The former is more time-consuming, while the latter is technically simpler and more often used. In both techniques, non-spherical markers with a size of approximately 1×3 mm have generally been used [10-17]. In contrast, true-spherical markers with 2.0-mm diameters

are used for automatic precise calculation of the gravity center of the marker in RAR for hepatic malignant tumors [18,19]. However, only a few studies with a small number of patients have assessed the safety and efficacy of percutaneous transhepatic marker implantation of true-spherical markers [18,19] and the complications and migration of true-spherical markers remain unclear.

This is the first study in which the efficacy and safety of percutaneous transhepatic implantation of true-spherical markers for RAR were evaluated with a sufficient number of patients for statistical analysis.

Materials and methods

Patients

Institutional review board approval was obtained for this retrospective review, and a Health Insurance Portability and Accountability Act waiver was granted.

Medical records of 148 patients who underwent percutaneous implantation of fiducial gold markers into the liver as preparation for RAR at our hospital from January 1999 to June 2016 were retrospectively reviewed. Of these patients, 48 were excluded for the following reasons: i) fluoroscopic images or computed tomography (CT) images were not acquired immediately post-procedure (n = 21), ii) no detailed procedure report

was available (n = 22), iii) radiation therapy was not performed in our hospital (n = 1), and iv) radiation therapy was cancelled due to the patients' poor general condition (n = 4). Consequently, 100 patients were evaluated in this study.

The patients included 73 men and 27 women (median age, 66 years; range, 38–89 years). All patients, except 1, had hepatobiliary cancers: 81 hepatocellular carcinomas, 15 metastatic hepatic tumors, and 3 intrahepatic cholangiocarcinoma. The remaining patient had extrahepatic lymph node metastasis of gastric cancer, close to the liver.

The indication of RAR for hepato-biliary cancers was as follows: i) Karnofsky performance status $\geq 70\%$, ii) Child–Pugh classification A or B, iii) tumor detectable on CT and/or magnetic resonance imaging (MRI), iv) 3 or fewer lesions without extrahepatic metastases, v) ineligible for, or refusal of any other locoregional therapy, e.g., surgery, radiofrequency ablation, and transcatheter arterial chemoembolization.

The type of radiation (X-ray or protons) used depended on tumor size, liver function, patients' health, and insurance coverage. In the patient with lymph node metastasis of gastric cancer, no hepatic metastasis was found, but RAR was indicated because this patient had sole lymph node metastasis in the para-aortic space. The liver was selected

as the site for implantation of the fiducial marker due to its proximity to the target lymph node.

Among 100 patients, 87, 11, and 2 patients had 1, 2, and 3 tumors, respectively (115 tumors in total). The median diameter of the target tumor was 24 mm (range: 7–154 mm). Tumor locations are summarized in Table 1.

For 115 tumors in 100 patients, 106 fiducial marker placements were initially planned, because radiation oncologists estimated that 1, 2, or 3 markers were needed for RAR of 103 tumors in 95 patients, 9 tumors in 4 patients, and 3 tumors in 1 patient, respectively. Only 1 marker was placed for 2 or more tumors when they were in close proximity.

RAR Equipment

The RAR systems employing implanted fiducial markers in our hospital are the real-time tumor-tracking radiotherapy (RTRT) system (Varian Medical Systems, Mitsubishi Electric, Tokyo, Japan) and real-time image-gated proton beam therapy (RGPT) system (Hitachi, Tokyo, Japan). They allow delivery of X-ray in RTRT and proton beam in RGPT when the implanted fiducial marker is within the gating window,

facilitating delivery of a precise radiation dose to the tumor while sparing the adjacent normal tissues.

Implantation procedure

All procedures were performed in the angiographic suite with a combined CT and angiography system (Artis zee TA, SOMATOM Definition AS64, Siemens, Munich, Germany). We aimed to implant the gold marker in the hepatic parenchyma within approximately ≤ 5 or 10 cm from the center of the tumor for RTRT or RGPT, respectively. When the tumor diameters exceeded 10 cm in RTRT, we implanted the gold marker as close to the tumor as possible. The location was chosen by consensus of the interventional radiologist(s) and radiation oncologist(s) prior to the procedure.

All marker implantations were performed, using Seldinger's method, by 7 board-certified interventional radiologists (with 5–20 years of experience in interventional radiology). A safe puncture tract, avoiding major vessels, was determined by liver ultrasonography; then, the liver parenchyma was percutaneously punctured under US guidance (Figure 1a), using an 18-gauge needle (Needle for Ultrasonically Guided Puncture, Create Medic, Kanagawa, Japan). Intra-procedural CT was performed

if the inserted needle tip was obscure, or the needle direction was uncertain under US-
or fluoroscopic-guidance alone.

A guidewire (0.035 Amplatz Ultra Stiff Wire Guide, Cook, Bloomington,
Indiana, USA, or 0.035 Fixed Core Wire 3-mm J Guide wire, Argon Medical Devices,
Dallas, Texas, USA) was inserted into the liver parenchyma through the needle (Figure
1b), followed by the introduction of a 2.55-mm-diameter sheath introducer (Introducer
Set, Medikit, Tokyo, Japan) (Figure 1c) designed for marker implantation (Figure 1d),
under X-ray fluoroscopic guidance. After removal of the guidewire and inner tube, the
absence of blood or bile juice reflux was confirmed through a 3-way stopcock of the
sheath with a 10-mL syringe, to ensure that the gold marker was not placed in the
vessels or bile duct. If reflux was observed, the sheath was pulled back or a gelatin
sponge torpedo (Spongel, Astellas Pharma, Tokyo, Japan) was introduced into the tip of
the sheath and the presence of reflux again checked. When reflux was absent, a 2-mm-
diameter, spherical, pure gold marker (iGold, Medikit, Tokyo, Japan) (Figure 1e) was
pushed into the liver parenchyma through the sheath, by means of the pusher (Figure
1f). The sheath was then extracted while packing the puncture tract with gelatine sponge
torpedoes. After removing the sheath, the site of the implanted marker was confirmed

on X-ray fluoroscopy (Figure 1g). Post-procedural CT was obtained if mispositioning or migration of the marker was of concern. If migration was confirmed on US, fluoroscopy, or CT, the complete procedure was repeated with an additional marker; such implantation was counted as an additional procedure in this study.

Finally, US was performed to confirm the absence of hemorrhage inside or on the surface of the liver, and the patient was placed on complete bed rest for 2 hours. On the day after the implantation procedure, contrast-enhanced planning CT (Figure 1h) was performed to evaluate the marker position and to monitor for complications, such as intra-abdominal hemorrhage. One day before the start of radiotherapy, diagnostic CT was performed to determine whether the marker was dislocated from its planned position in RGPT. This was followed by abdominal fluoroscopic imaging and/or set-up imaging at each fraction on RAR to check the marker position.

Evaluation of efficacy and safety

Technical and clinical success rates were evaluated. Technical success was defined as completion of gold marker implantation into the hepatic parenchyma. When migration occurred, the implantation procedure was defined as a technical failure. “Migration” was defined as migration of the gold marker from the initial site of

implantation in the hepatic parenchyma to other sites, such as the extra-hepatic region or intrahepatic vessels (portal vein, hepatic vein, or bile duct). Migration was categorized as intraprocedural migration when it was recognized during the implantation procedure, and as delayed migration when it was recognized after the procedure. Delayed migration was detected during the daily set-up of patients for radiotherapy. After alignment of the patient on the treatment couch, using a bony structure for reference in orthogonal X-ray imaging, the 3D position of the marker and its trajectory relative to the bony structure were checked using 2 sets of orthogonal fluoroscopy imaging. If the dislocation of the marker from its planned position exceeded 2 mm, even after several manual maneuvers, such as re-arranging the patient's body or instructing the patient to stand upright for a period of time, the patient underwent additional CT scanning to check for delayed migration.

Technical marker placement success was evaluated by a board-certified interventional radiologist, based on post-procedural CT or planning CT. Migration was checked during and after the implantation procedure until all RAR sessions had been completed. The technical success rate per procedure was calculated. The causes of migration were also assessed according to medical records.

213 Clinical success was defined as completion of successful tracking of the
214 implanted gold marker and planned RAR. When the implanted marker could not be
215 utilized for tracking, the marker implantation was defined as a clinical failure.

216 Complications after percutaneous marker implantation procedure were recorded
217 according to the information obtained from the referring physician and medical records.
218 These complications were evaluated based on the Common Terminology Criteria for
219 Adverse Events v4.0 (CTCAE). Minor complications were defined as CTCAE grades 1
220 and 2, and major complications were defined as grade 3 or higher.

221 **Results**

222 ***Technical Success***

223 Of the 106 planned fiducial marker implantations, 98 (92.5%) 1st implantations
224 were successful, without migration (Figure 2), while 8 migrated. Of these 98
225 implantations, 2 patients underwent successful 2nd marker implantations during the
226 same session because mispositioning of the 1st implanted marker was a concern for the
227 attending physician. Four markers were implanted in the extra-hepatic region and
228 another 4 markers migrated from the initial implantation site in the hepatic parenchyma,
229 to the portal vein in 1, the hepatic vein in 1, and the bile duct in 2 patients. Of these 8

230 migrations, 6 were confirmed intraprocedurally, and the 2 migrations into the bile duct
231 were delayed.

232 In the 6 intraprocedural migrations, successful 2nd marker implantation was
233 performed in 5 cases. In the remaining patient, the marker was confirmed to be located
234 in the intrahepatic portal vein at the periphery of hepatic segment 3; no additional
235 marker was implanted, because the marker position (in a small portal vein) was
236 expected to be stable.

237 Delayed migration of 2 markers into the bile duct were diagnosed 1 and 14 days
238 post-procedurally, although the operator initially considered the marker implantations
239 successful. A 2nd marker implantation was successfully performed in 1 patient. The
240 other patient underwent 2nd marker implantation; however, the marker migrated into the
241 hepatic vein. A 3rd marker was then successfully implanted during the same session.

242 In summary, 106 procedures were initially planned; the initial success rate was
243 92.5% (98/106); 2nd and 3rd procedures were planned for 9 and 1 markers, respectively,
244 and 116 procedures were conducted in total. Of these, 107 markers were successfully
245 implanted at the hepatic parenchyma without migration, in 1–3 implantation
246 procedure(s). Thus, the technical success rate per procedure was estimated as 92.2%.

247 Among the 116 markers, 9 implantations were technical failures (due to migration).
248 Nine of the 116 (7.8%) implanted markers migrated; 8 and 1 migrations occurred at the
249 1st and 2nd implantation procedures, respectively. Four markers were implanted into the
250 extra-hepatic region because of the unexpected dislocation of the sheath introducer, due
251 to respiratory movement during the procedure. Migration into the portal vein and
252 hepatic vein occurred when the sheath was extracted during packing of the puncture
253 tract. For the remaining 3 markers, the reasons for migration were unknown, due to lack
254 of detailed medical records.

255 ***Clinical Success***

256 Among 115 tumors in 100 patients, all implanted markers were successfully
257 tracked by the RTRT or RGPT systems and the planned treatment was completed.
258 Accordingly, the clinical success rate was 100% (115/115) per tumor and 100%
259 (100/100) per patient.

260 ***Complications/Adverse Events***

261 Among the 100 patients, abdominal pain after the procedure occurred in 16
262 patients (grade 1 in 6 patients, grade 2 in 10 patients), mild fever occurred in 7 (all

grade 1), hemorrhage occurred in 7 (all grade 1), and pneumothorax occurred in 1 patient (grade 1). All adverse events were treated conservatively. Blood transfusion and chest tube insertion were not necessary. No major complications occurred. No complications associated with migrated markers were observed up to the end of RAR, although the migrated markers were not retrieved.

Discussion

Percutaneous implantation of fiducial marker(s) is simple, can be easy and rapidly performed, and is widely accepted as a routine practice for improving accuracy [13,16]. Non-spherical fiducial gold markers (Figure 3) can be simply implanted by pushing the marker into the liver parenchyma through a needle (typically 14–25-gauge) [13, 14] inserted into the liver (Figure 4) [11, 14, 15]. A high technical success rate of 97.3%–100% has been reported for percutaneous implantation of hepatic non-spherical fiducial markers (Figure 3) [11, 14, 15, 20]. In contrast, implanting a 2-mm-diameter, true-spherical gold marker requires insertion of a sheath (2.55-mm-diameter) specifically designed for marker implantation after insertion of the needle into the liver [18]. This is the first study to demonstrate a high technical success rate for implantation of true-spherical fiducial markers (92.2%) with a relatively large number of patients.

The migration rate of spherical markers was 7.8% (9/116), which is higher than that reported previously for non-spherical fiducial markers (0.9%–1.5%) [12, 17]. Four of 9 migrating markers in our study involved dislocation of the sheath introducer due to respiratory organ movement. Accordingly, use of a sheath introducer could lower the technical success rate. Avoiding dislocation may require insertion of the sheath introducer as deeply as possible, with a long intrahepatic tract, to stabilize it against respiratory motion. The remaining 5 markers migrated into intrahepatic vessels. The proximity of the tumor to a major hepatic vein could cause migration [21]. Additionally, the shape of true-spherical markers may facilitate migration. We observed 2 migrations when the sheath was extracted while packing the puncture tract with gelatine sponge torpedoes. If a marker migrates into the right atrium, it should be retrieved because it can cause arrhythmia [21] or systemic embolization in patients with right-to-left cardiac shunting [22]. However, we did not experience any migration-associated complications.

Chan et al. compared visibility of various implantable non-spherical markers [23] and concluded that, for IGRT, markers with at least a 0.75-mm diameter should be selected for hybrid kilovoltage (kV)/mV imaging (the worst condition for marker visualization). Because non-spherical markers are usually tiny cylinders with a small

297 short-axis diameter (0.75–1.1 mm), they may be poorly visible on X-ray images,
298 especially when they are projected in the short-axis plane in patients who are obese or
299 muscular and may not be useful for tracking of markers in RAR, such as in RTRT and
300 RGPT.

301 A 2-mm-diameter, true-spherical, pure gold marker has much better visibility
302 than non-spherical markers due to its larger diameter [11, 13-16]. Therefore, the
303 technical success rate (per procedure) and complication rate in this study, which was
304 slightly worse than those reported previously for non-spherical markers
305 [11,12,14,15,17], seems acceptable, as this true-spherical marker theoretically provides
306 the best likelihood of usability for tumor tracking. The accuracy in calculating the 3D
307 co-ordinates of the gravity center of a marker is logically better with a spherical marker
308 than with a non-spherical marker [24].

309 Implantation of 3 or more markers is usually required per patient [13]. Although
310 multiple fiducial markers can be beneficial for localizing the target, they produce more
311 unfavorable artifacts in CT scans, which may affect the target volume delineation and
312 dose calculation. We implanted 116 true-spherical markers in 100 patients with 115
313 lesions (1.2 and 1.0 markers per patient and per lesion, respectively), while Jarraya et al.

314 implanted 1444 non-spherical markers in 328 patients with 424 hepatic lesions (4.4 and
315 3.4 markers per patient and per hepatic lesion, respectively) [17]. Making multiple liver
316 punctures for implanting multiple markers are potentially time-consuming and more
317 invasive. Therefore, our technical success rate was reasonable. If markers are placed
318 within 2 mm from their planned positions in RTRT and RGPT, use of multiple markers
319 has no added benefit. However, if irradiation of the tumor involves dynamic direction
320 changes of the therapeutic beam, multiple markers will be required to adjust for rotation
321 and distortion of the tumor during respiration.

322 Percutaneous fiducial marker placement is associated with complication risks
323 [12,13], such as major bleeding or sepsis, at a reported rate of 1.6% after marker
324 placement in the abdomen or pelvis [12]. A lower major complication rate of 0.6%
325 (pneumothorax and biloma in 1 patient each) has been reported for marker placement in
326 the liver [17]. However, we encountered only minor complications: 7 mild fevers, 7
327 hemorrhages, and 1 pneumothorax, which were all conservatively treated. Therefore,
328 we consider our technique to be safe.

329 In future, the development of spherical or semi-spherical gold markers that can
330 be implanted by a simple needle insertion technique, such as that used for non-spherical

markers, while preserving visibility similar to that of a 2-mm-diameter, true-spherical, pure gold marker, may yield a higher success rate with less invasiveness, and a lower complication rate.

This study had several limitations. First, it was retrospective in nature. Second, approximately one-third of patients who underwent marker implantation were excluded due to lack of imaging data and/or procedure reports. Third, implantation procedure details might have changed between the initial and later phases, because different physicians were involved. These factors could affect estimation of the success and complication rates. For the assessment of delayed migration, diagnostic CT was performed to check whether the marker was dislocated from its planned position in RGPT, 1 day before the start of RGPT, but not in RTRT, during this period. We now recommend CT evaluation for delayed migration 1 day before either RGPT or RTRT [25].

There are high expectations regarding RAR without fiducial markers, such as on-line MRI in the treatment room, for the treatment of liver tumors. However, only 2-dimensional MRI movies have been used thus far [26]. In addition, automatic real-time contouring of liver tumors with MRI are not always sufficiently accurate for automatic

348 gating of irradiation [26]. Therefore, it remains important to implant fiducial markers
349 into the liver in real-world RAR.

350 In conclusion, percutaneous transhepatic implantation of true-spherical gold
351 markers facilitate RAR; it is technically feasible and can be conducted with a
352 reasonably high success rate and low complication rate by interventional radiologists.

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355

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Figure Legends

Figure 1 Procedure of percutaneous transhepatic implantation of true-spherical gold marker. **(a)**

Safe puncture tract (white arrows) is decided by scanning of the liver with ultrasonography

(US). **(b)** Fluoroscopic image shows insertion of the 0.035-inch guidewire (black arrow head)

through an 18-gauge needle (black arrows) percutaneously punctured with US guidance. **(c)**

Digital photograph shows a percutaneously placed 2.55-mm diameter sheath introducer (black

arrow) after removal of the guidewire and inner tube. **(d)** Digital photograph shows a 2.55-mm

diameter sheath introducer (Introducer Set, Medikit, Tokyo, Japan) (white arrow) designed for

marker implantation, and the pusher (white arrowhead). **(e)** Digital photograph shows a 2-mm

diameter spherical pure gold marker (iGold, Medikit, Tokyo, Japan) close to the tip of the

sheath introducer, which has a radiopaque marker (white arrow). **(f)** A 2-mm-diameter,

spherical pure gold marker is pushed into the liver parenchyma through the sheath (black arrow)

by means of the pusher (black arrowhead). **(g)** Fluoroscopic image shows the true-spherical

fiducial marker implanted in the liver parenchyma (white arrowhead). **(h)** Contrast enhanced-

computed tomography for planning of real-time adaptive radiotherapy (RAR), obtained 1 day

after marker implantation to evaluate the marker position, shows true-spherical fiducial marker

(black arrow) in the liver parenchyma.

454 **Figure 2** Details of marker malposition.

455 **Figure 3** Various non-spherical fiducial markers for image-guided radiation therapy (IGRT).

456 **Figure 4** A representative non-spherical fiducial marker and its implantation system.

457 **(a)** A 1.1-mm-diameter, 10-mm-long non-spherical fiducial marker (Visicoil, IBA Dosimetry,

458 Schwarzenbruck, Germany) (single asterisk) is composed of a kit with a 17-gauge needle (white

459 arrow), inner stylet (white arrowhead), and the stopper (double asterisk). **(b)** A marker is set at

460 the needle tip and the marker kit is assembled for the percutaneous implantation procedure. **(c)**

461 The stopper is removed when the tip of the needle reaches the target site. Next, the needle is

462 pulled over the inner stylet, holding the inner stylet in place. **(d)** The marker set at the needle tip

463 is placed in the target site by pushing the inner stylet.

464

Table 1. Tumor locations

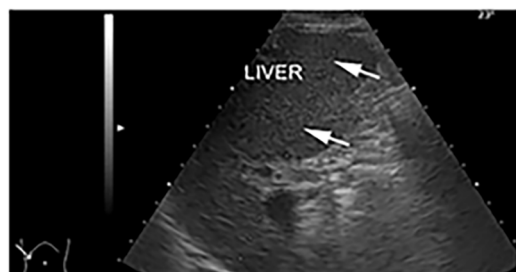
Location of target tumors	Number of tumors
S1	9
S2	5
S3	11
S4	14
S5	9
S6	6
S7	5
S8	24
Right lobe (> 2 segments)	15
Left lobe (> 2 segments)	7
Portal vein tumor thrombus	8
Hepatic vein tumor thrombus	1
Lymph node metastasis	1

S1 = caudate lobe; S2 = dorsolateral segment of left lobe; S3 = ventrolateral segment of left lobe; S4 =

medial segment of left lobel S5 = anteroinferior segment of right lobe; S6 = posteroinferior segment of

right lobe; S7 = posterosuperior segment of right lobe; S8 = anterosuperior segment of right lobe.

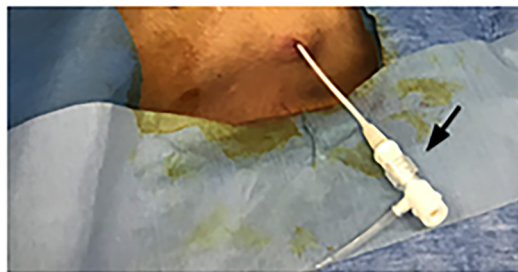
Figure 1



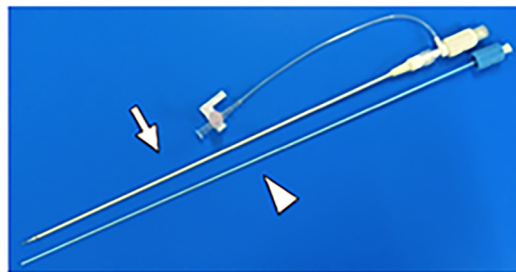
a.



b.



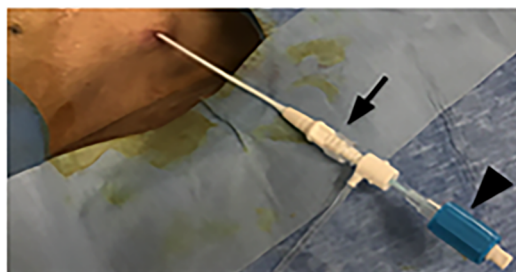
c.



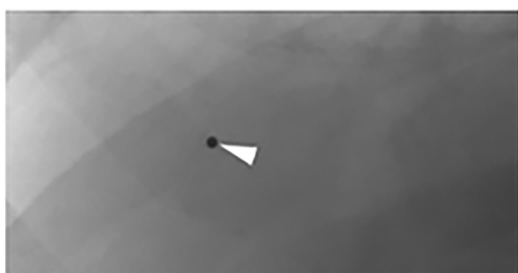
d.



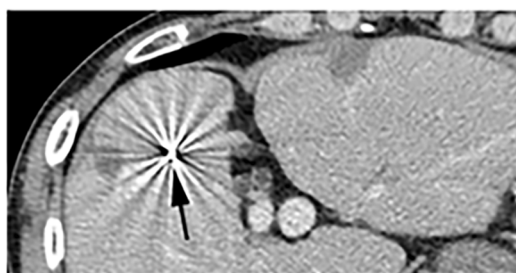
e.



f.



g.



h.

Figure 2

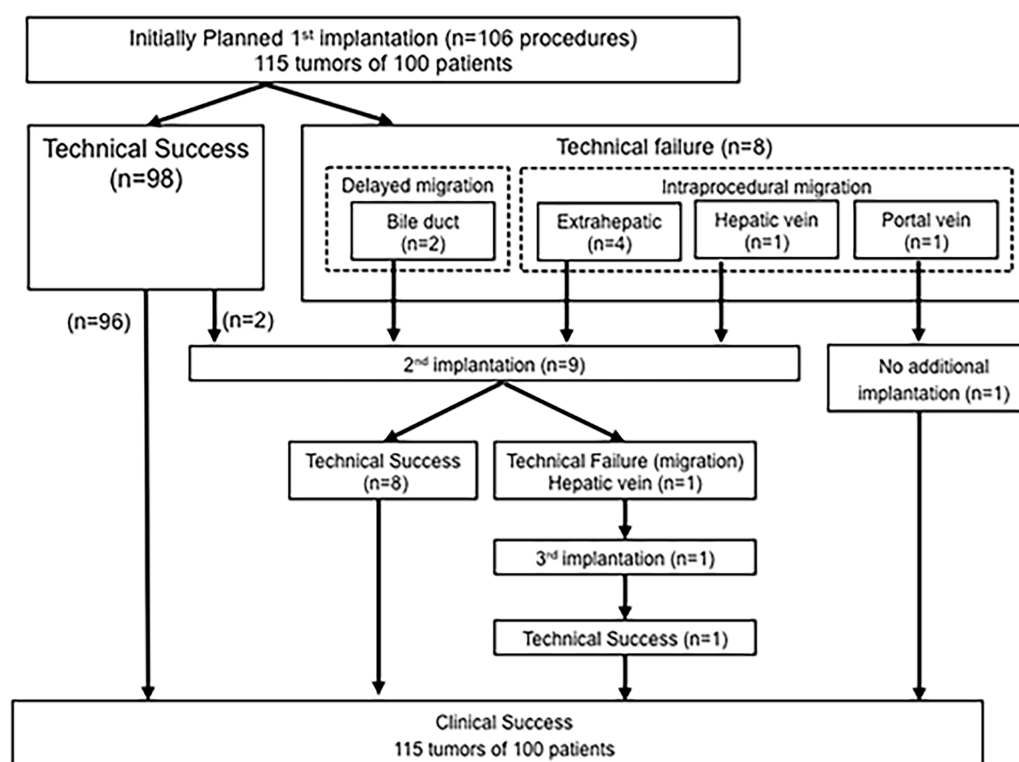
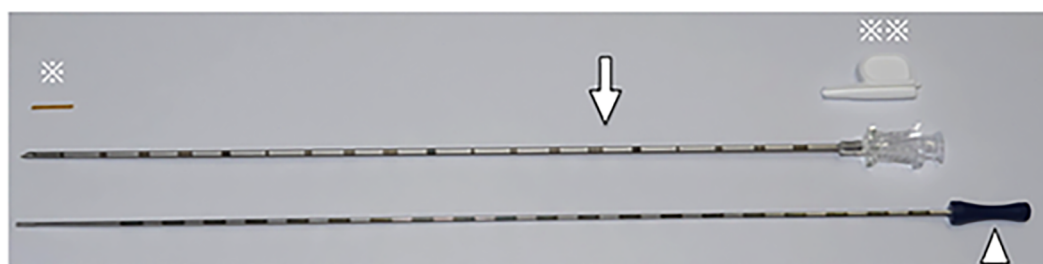


Figure 3



Figure 4



a.



b.



c.



d.