Hepatocellular carcinoma effective stereotactic body radiotherapy using Gold Anchor and the Synchrony system: Two case reports and review of literature

Sakue Masuda, Toshitaka Tsukiyama, Yumiko Minagawa, Kazuya Koizumi, Makoto Kako, Takeshi Kinbara, Uojima Haruki

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Abstract

BACKGROUND
Radiotherapy for hepatocellular carcinoma (HCC) is considered to have limited efficacy because of treatment intensity considering that the irradiated area includes the liver, which is highly radiosensitive. In this report, we present two cases in which tumor control by surgical resection, radiofrequency ablation, transcatheter arterial chemoembolization (TACE), and lenvatinib administration was difficult, but stereotactic body radiotherapy (SBRT) using the Synchrony system by Radixact™ and Gold Anchor® (GA) was effective.

CASE SUMMARY
A 60-year-old man had a single 10-cm HCC in the right lobe. Viable lesions remained after TACE, and levels of alpha-fetoprotein and protein induced by vitamin K antagonists II (PIVKA-II) decreased and quickly re-elevated. We performed SBRT with GA. Three weeks after implantation, localized radiotherapy (SBRT; 40 Gy/5 fractions) was performed using the Synchrony system by Radixact™. Four weeks later, the viable lesion had disappeared, and the PIVKA-II levels decreased. A 77-year-old man had a single 12-cm HCC in the right lobe. The patient experienced recurrence after hepatectomy. Further recurrence occurred after TACE, and we performed SBRT with GA. Because of the proximity of the HCC to the gastrointestinal tract, localized radiotherapy (SBRT; 39 Gy/13 fractions) to the HCC was performed 3 wk after implantation using the Synchrony system by Radixact™ and GA was effective.
system by Radixact™. Four weeks later, the viable lesion had disappeared on computed tomography, and the PIVKA-II levels decreased.

CONCLUSION

SBRT using the Synchrony system and GA can deliver a large dose accurately and safely, and could have a high therapeutic effect.

Key Words: Fiducial marker; Hepatocellular carcinoma; Gold Anchor®; Radixact™; Stereotactic body radiotherapy; Case report

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Core Tip: Radiotherapy using fiducial markers has been performed for hepatocellular carcinoma (HCC) for several years. However, the Gold Anchor® (GA) used in this report is a new fiducial marker with a small diameter, which is expected to reduce the incidence of complications. The Synchrony system by Radixact™ is also a new radiation device, which is useful in respiratory motion management and allows complete tracking of the HCC in which the GA is implanted. Radiotherapy using these devices was highly effective for HCC that could not be controlled by surgery, transcatheter arterial chemoembolization, or molecular targeted drugs.

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INTRODUCTION

Hepatocellular carcinoma (HCC) ranks as the sixth cause of cancer incidence and the fourth cause of cancer-related deaths worldwide[1]. There are various treatment methods for HCC, including surgical resection, radiofrequency ablation (RFA), transcatheter arterial chemoembolization (TACE), systemic chemotherapy, and radiotherapy[2]. Since the major risk factors for HCC include chronic hepatitis and liver cirrhosis, many patients have an underlying liver disease at the time of treatment. In addition to tumor and technical factors, the patient's liver function has a significant impact on determining the optimal treatment for HCC. Delis et al[3] and Bruix et al[4] reported that only 10%-30% of HCC cases are indicative of curative surgery because most HCC is diagnosed at intermediate or advanced stages. Radiotherapy is not included in the Barcelona Clinic Liver Cancer staging treatment allocation scheme; however, evidence showing that radiotherapy may be a potential tool for primary treatment or for bridging/downsizing purposes is growing[5]. A variety of technological progress has led to more accurate and dose-escalated radiotherapy, particularly stereotactic body radiation therapy (SBRT)[6]. SBRT sufficiently reduces the dose to adjacent organs due to its sharp dose fall-down outside of the target, while enhancing the biological effectiveness of a large single dose[7]. However, with SBRT it can be difficult to track tumors in the liver due to respiratory motion management (RMM)[8]. SBRT with RMM is becoming more common; however, RMM is often performed with breath-holding or fixation of the trunk. For a more focused and accurate delivery of SBRT, fiducial markers are used to locate tumors in the liver[9]. Using Gold Anchor® (GA) (Naslund Medical AB, Huddinge, Sweden), a new marker of fine diameter, we performed SBRT in two cases and thereby confirmed its efficacy. The GA used in these cases is characterized by a low risk of complications and high visibility on computed tomography (CT) and magnetic resonance imaging (MRI)[9].

CASE PRESENTATION

Chief complaints
Case 1: For treatment of HCC.
Case 2: For further management of HCC.
**History of present illness**

**Case 1:** The patient was a 60-year-old man with alcoholic cirrhosis. For three years, he underwent regular CT examinations annually, and CT revealed a single 10-cm HCC in the right lobe (Figure 1A).

**Case 2:** The patient was a 77-year-old man with hepatitis B infection. He underwent regular CT examinations annually at a nearby hospital. Four years ago, CT revealed a single HCC measuring 12-cm in the right lobe (Figure 2A). The patient underwent hepatectomy at the same institution, but recurrence occurred (Figure 2B). TACE was then performed to treat the recurrence; however, there was further recurrence (Figure 2C). The patient was subsequently admitted to our hospital for further management of the HCC.

**History of past illness**

**Case 1:** The patient was diagnosed with hypertension, diabetes, and gout 10 years ago, and with alcoholic cirrhosis and angina 3 years ago. He had been taking the following medications: Telmisartan, amlodipine basilate, febuxostat, empagliflozin linagliptin, aspirin, pitavastatin calcium hydrate, and diltiazem hydrochloride.

**Case 2:** The patient was diagnosed with hepatitis B seven years ago at a nearby hospital. He was previously diagnosed with benign prostatic hyperplasia. He was not on any medication.

**Personal and family history**

**Case 1:** He had been drinking 50-100 g of alcohol daily for 40 years.

**Case 2:** He rarely drank. He was exposed to the atomic bomb in World War II.

**Physical examination**

**Cases 1 and 2:** There were no findings of anemia or jaundice. The abdominal findings were also unremarkable.

**Laboratory examinations**

**Case 1:** Blood tests showed negative hepatitis virus markers (Table 1), and Child-Pugh status was A.

**Case 2:** Blood tests were positive for hepatitis B core antibody (Table 1), and Child-Pugh status was A.

**Imaging examinations**

**Case 1:** Contrast-enhanced CT revealed a typical 10-cm HCC in the right lobe. The contrast enhanced the HCC in the early phase and washed out in the late phase (Figure 1A).

**Case 2:** Contrast-enhanced CT revealed a typical 12-cm HCC in the right lobe. The contrast stained the HCC in the early phase and washed out in late phase (Figure 2A).

**FINAL DIAGNOSIS**

**Case 1**
The final diagnosis was HCC due to alcoholic liver cirrhosis.

**Case 2**
The final diagnosis was HCC due to hepatitis B infection.

**TREATMENT**

**Case 1**
TACE was performed twice for HCC, but in both instances, viable lesions remained, and levels of alpha-fetoprotein and protein induced by vitamin K antagonists-II (PIVKA-II) decreased then quickly re-elevated. A third TACE was performed; however, the results were similar to the previous TACEs: 2.5 cm of viable lesions remained, and the once-decreased PIVKA-II level immediately increased again (Figure 1B-D). Therefore, we decided to perform SBRT with GA; an interventional radiology specialist with 30 years of experience selected a 22G needle and implanted two GAs within 2 cm of the HCC (Figure 3). One week after implantation, CT registration was performed, and radiotherapy was planned. Three weeks after implantation, localized radiotherapy (SBRT; 40 Gy/5 fractions) was performed for HCC using the Synchrony system by Radixact™ (Accuray Japan K.K., Tokyo, Japan).
**Case 2**

We performed TACE twice for HCC in our hospital, but both times viable lesions remained. The PIVKA-II level decreased but quickly re-elevated. A third TACE was performed; however, the results were similar to the previous TACEs: 2 cm of viable lesions remained, and the decreased PIVKA-II level increased again (Figure 2D and E). Therefore, we decided to perform SBRT with GA, and two GAs were implanted within 2 cm of the HCC with a 22G needle. In this case, the biloma was complicated after hepatectomy at the previous hospital, and the puncture route for GA implantation passed near the site (Figure 4). One week after implantation, CT registration was performed, and radiotherapy was planned. Because of the proximity of the HCC to the gastrointestinal tract, localized radiotherapy (SBRT; 39 Gy/13 fractions) to the HCC was performed 3 wk after implantation using the Synchrony system by Radixact™.

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**OUTCOME AND FOLLOW-UP**

**Case 1**

Four weeks later, CT showed that the viable lesion had disappeared and the PIVKA-II levels decreased (Figure 5). There were no complications of grade 3 or higher during the clinical course (Figure 6). No
Figure 1 Computed tomography of case 1. A: On admission; B: After the first transcatheter arterial chemoembolization (TACE); C: After the second TACE; D: After the third TACE. Orange arrowhead: Hepatocellular carcinoma before TACE; yellow arrowhead: Viable lesion after TACE.

Figure 2 Computed tomography in case 2. A: Before surgical resection at a nearby hospital; B: At the time of recurrence; C: Before Transcatheter arterial chemoembolization (TACE) at our hospital; D: After the first TACE at our hospital; E: After the third TACE at our hospital. Orange arrowhead: Hepatocellular carcinoma (HCC) before surgical resection at a nearby hospital; blue arrowhead: recurrence of HCC; yellow arrowhead: Viable lesion after TACE.

recurrence has been observed at 9 mo after SBRT with GA.

Case 2
Four weeks later, the viable lesion had disappeared on CT and the PIVKA-II levels decreased (Figure 7). In this case, the puncture route for GA implantation passed near the biloma. As a result, the biloma developed complications from infection (Figure 8), which improved through conservative treatment. There were no other complications of grade 3 or higher during the clinical course (Figure 9). Recurrence occurred 7 mo after SBRT with GA; however, without the short-term recurrence seen after TACE, progression-free survival was longer with this treatment.

DISCUSSION
Regarding early-stage HCC, it is standard to undergo curative treatments, such as surgical resection (partial liver resection or liver transplantation) and percutaneous ablation, most commonly RFA. Regarding intermediate-stage HCC, many patients undergo TACE as their first local regional treatment [5,8]. However, such treatments have limitations in locally advanced cases. For example, TACE is contraindicated in cases with portal vein thrombosis, malignant portal vein thrombosis, and untreatable arteriovenous fistula. RFA is contraindicated in cases with bleeding disorders and can be difficult in tumors near the diaphragm, digestive tract, pancreas, hepatic hilum, and major bile ducts or vessels.
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Figure 3 Gold Anchor® placement in case 1. Orange arrowhead: Gold Anchor® (GA); yellow arrowhead: Puncture needle of GA.

Figure 4 Gold Anchor® placement in case 2. A and B: Blue arrowhead; Biloma complicated with surgical resection at the previous hospital, white arrow; Ethyl ester of iodinated poppyseed oil fatty acid (lipiodol) after Transcatheter arterial chemoembolization, C: white arrow; Ethyl ester of iodinated poppyseed oil fatty acid (lipiodol) after Transcatheter arterial chemoembolization, yellow arrowhead; Puncture needle of GA, D and E: Orange arrowhead; Gold Anchor® (GA), white arrow; Ethyl ester of iodinated poppyseed oil fatty acid (lipiodol) after Transcatheter arterial chemoembolization.

[10]. Furthermore, Lin et al.[11] reported that RFA was less effective for HCCs larger than 4 cm. Patients who do not satisfy the Milan criteria or San Francisco criteria are not commonly indicated for surgical resection[5]. It has also been reported that patients with intermediate- to advanced-stage HCC have a high recurrence rates. Five-year tumor recurrence rates after surgical resection and RFA may be more than 50% and up to 80%, respectively. These high recurrence rates include patients who undergo TACE [8,12]. In our case, one patient had a recurrence after surgery and again after TACE. In the other case, recurrence occurred after TACE. Bearing in mind the aforementioned reasons, as well as the fact that radiotherapy is constantly evolving due to technological innovation, radiotherapy is expected to be the fourth local therapy available for HCC[5,8,10].

Currently, there are useful treatment guidelines for managing HCC from America[13,14], Europe [15], Japan[16], Korea[17], China[18], and Taiwan[19]. There is a variety of evidence on the efficacy of radiotherapy for HCC, but phase III randomized trials are lacking. Therefore, based on the current guidelines, radiation therapy is not mentioned or is listed as having a limited role. However, modern radiotherapy has become increasingly important in the management of patients with HCC due to two
Figure 5 Computed tomography before and after stereotactic body radiation in case 1. Yellow arrowhead: Viable lesion after the third transcatheter arterial chemoembolization; blue arrowhead: Disappearance of the contrast effect of the tumor after stereotactic body radiation.

Figure 6 Clinical course in case 1. Orange arrows: Viable lesion; blue arrows: Disappearance of the contrast effect of the tumor after stereotactic body radiation. AFP: Alpha-fetoprotein; PIVKA-II: Protein induced by vitamin K antagonists-II; SBRT: Stereotactic body radiation; TACE: Transcatheter arterial chemoembolization.

changes. First, advances in radiotherapy techniques, for example SBRT and proton therapy, have allowed for more accurate delivery of radiation to enhance tumor control and reduce complications in organ close to the HCC. Second, the development of molecular targeted drugs and checkpoint-blockade immunotherapy has prolonged the overall survival of patients with HCC, reaffirming the importance of local tumor control. In this regard, several clinical trials of SBRT for HCC are underway\[8,10\]. The reason for choosing radiotherapy in the present cases was that they showed local recurrence and were refractory to surgery, TACE, or chemotherapy; in addition, RFA was difficult because, in the first case, the recurrence was close to the inferior vena cava, whereas in the second case, it was close to the left branch of the portal vein.

SBRT builds on the principle of delivering high doses per fraction using steep dose gradients and smaller margins of uncertainty. A large dose of radiation is typically defined as one over 2 Gy. SBRT delivers extremely precise high doses in a limited number of treatment fractions (usually 3-6 fractions at > 5 Gy per fraction) over a treatment course of 1-2 wk\[8\]. High doses of radiation in a few fractions
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Figure 7 Computed tomography before and after stereotactic body radiation. A: Computed tomography (CT) before stereotactic body radiation (SBRT); B: CT after SBRT. Yellow arrowhead: Viable lesion after the third transcatheter arterial chemoembolization; blue arrowhead: Disappearance of the contrast effect of the tumor after SBRT.

Figure 8 Computed tomography of infected biloma. Blue arrows: Infected biloma.

allows for a higher proportion of cancer cell death while reducing the chance of tumor DNA repair or repopulation[5]. Kim et al[20] reported that patients in the high-dose group achieved higher relative objective responses. To deliver high doses safely, image guidance and RMM are required. However, it is difficult to track a tumor in the liver during radiotherapy. Therefore, fiducial markers are used to track tumors in the liver. RMM using the Synchrony system with Radixact™ in combination with fiducial markers has higher accuracy and shorter irradiation time than other RMMs. The irradiation area to normal liver tissue is narrow, the treatment time is short, and posture maintenance is easy since it tracks HCC under free breathing. This makes it easier to deal with patients with impaired liver function and older patients who have difficulty maintaining a posture for a long time. SBRT with GA and Radixact™ is advantageous for HCC, which is more dose-dependent than several other organ cancers, and for
normal liver cells, which are more radiosensitive than the lung[21,22].

There are no complications specific to Radixact™, but specific complications associated with SBRT and GA should be considered. Commonly used fiducial markers are 0.35-1.1 mm in diameter. Larger markers are relatively easy to identify on CT or MRI. However, larger needle diameters increase the frequency of implantation metastases, bleeding, and the occurrence of serious complications[23,24]. In addition, the risk of bleeding is particularly high in patients with cirrhosis. Major complications after fiducial marker placement include pain, migration of fiducial markers, implantation of metastases, bleeding, and infection. Although the rate of complications is 12%-14%, complications other than pain are rare[25,26]. However, the fiducial marker is a relatively new method for HCC, and the accumulation of data is still limited. Referring to the data of percutaneous image-guided liver biopsy with comparable puncture needle thickness, the rate of implantation metastases was 3%, of bleeding was 2%, and of infection was 0.35%[23,24,27]. In fiducial markers, the tumor itself is not punctured; therefore, the risk of implantation metastases is expected to be lower than that of percutaneous image-guided liver biopsy. In one of our cases, the puncture route was in the vicinity of a biloma complicated by surgical resection which led to infection of the biloma. Although complications of infection due to fiducial marker placement are very rare, care should be taken when there is a biloma on the puncture route. In this case, we believe that infection could have been avoided by changing the puncture route.

The GA used in this study is characterized by its small diameter which can reduce the risk of complications. Another feature is that the GA can be implanted in a zigzag or spherical shape owing to its concavo-convex shape, and pure gold contains 0.5% pure iron, which results in low migration and highly visibility on CT and MRI[9].

Ultrasound-guided placement, CT-guided placement, and endoscopic ultrasound-guided placement have been performed, and each method has the same success and complication rates[25,28,29]. Because of the risk of fiducial marker migration, multiple implantations are recommended. Placing the fiducial markers in close proximity to each other or on the same plane of the CT may cause the irradiator to misidentify them during radiation therapy. Therefore, we performed CT-guided placement to improve the accuracy of GA placement.

One of the advantages of SBRT over conventional radiotherapy is that the total dose to adjacent organs is low owing to the rapid dose fall-off inherent in SBRT. Nonetheless, even with SBRT, potential liver-related toxicities include sequelae associated with radiation-induced liver disease (RILD), including fatigue, abdominal pain, ectopic hepatomegaly, ascites, and elevated liver enzymes, which can usually develop within 4 months of radiotherapy[10]. In addition to these findings, patients may also experience jaundice, thrombocytopenia, and changes in coagulation factors. A review of the prospective literature shows that adverse events of grade 3 or higher are rare, with most studies reporting less than 12%[5]. It should be noted that patients with a Child-Pugh classification of B7 or lower have a lower risk of RILD compared to patients with a Child-Pugh classification of B8 or higher.
In our cases, no RILD was observed even 4 mo after SBRT. Another report stated that the concurrent use of SBRT with sorafenib should be avoided because it is likely to cause grade 3 gastrointestinal disorders and tumor rupture[31]. Therefore, lenvatinib, a molecular targeted drug similar to sorafenib, was discontinued during the SBRT treatment period in our cases.

As described above, SBRT with GA and the Synchrony system can be considered a useful fourth local therapy for HCC. However, the irradiation range is limited by the patients’ liver function; in the literature, most patients treated with SBRT have Child-Pugh classification of A and have a few tumors (often < 3 tumors)[32].

**CONCLUSION**

SBRT combined with GA and the Synchrony system by Radixact™ is minimally invasive, highly accurate, and can deliver a large dose of radiation to HCC.

In our cases, tumor control was difficult with surgery, TACE, or molecular targeted drugs; however, SBRT combined with GA and the Synchrony system by Radixact™ was highly effective for HCC. The GA used in this report is a new fiducial marker with a small diameter which is expected to reduce the incidence of complications. The Synchrony system by Radixact™ is also a new radiation device that is useful in RMM and allows complete tracking of the HCC in which the GA is implanted.

The method and systems used in this study are considered safe and effective, and we would like to use them in future work for the treatment of HCC in which tumor control by surgical resection, RFA, TACE, and molecular targeted drug administration is difficult. However, this is a case report and further research, such as phase III trials, is needed.

**FOOTNOTES**

**Author contributions:** Masuda S, Koizumi K, Kako M, Kinbara T, and Uojima H were the patient’s hepatologists, reviewed the literature, and contributed to manuscript drafting; Masuda S and Minagawa Y reviewed the literature and contributed to manuscript drafting; Tsukiyama T and Minagawa Y were the radiologists and performed the radiotherapy and contributed to manuscript drafting; Tsukiyama T analyzed and interpreted the imaging findings; Masuda S, Uojima H, Tsukiyama T, and Minagawa Y were responsible for the revision of the manuscript and for important intellectual content; all authors issued final approval for the version to be submitted.

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**Country/Territory of origin:** Japan

**ORCID number:** Sakue Masuda 0000-0002-8127-0154; Toshitaka Tsukiyama 0000-0003-0310-8204; Yumiko Minagawa 0000-0002-4420-8079; Kazuya Koizumi 0000-0002-3677-5030; Makoto Kako 0000-0002-6447-8471; Takeshi Kinbara 0000-0002-8229-2638; Uojima Haruki 0000-0003-1719-1352.

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