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Scientific Article

Transarterial Chemoembolization with LC Bead LUMI followed by Stereotactic Body Radiation Therapy in Treatment of Hepatocellular Carcinoma

Evrosina I. Isaac, BS,[a] Jacob Hall, MD,[b] Joshua B. Dault, MD,[c] Jeffrey Elbich, MD,[d] Adrienne McGhee, RRA,[d] and Emma C. Fields, MD[c,*]

[a]*Virginia Commonwealth University, School of Medicine, Richmond, Virginia;* [b]*Department of Radiation Oncology, University of North Carolina, Chapel Hill, North Carolina;* [c]*Department of Radiation Oncology, Virginia Commonwealth University Health System, Richmond, Virginia;* [d]*Department of Radiology, Vascular Interventional Radiology, Virginia Commonwealth University Health System, Richmond, Virginia*

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Abstract

Purpose: Transarterial chemoembolization (TACE) in combination with stereotactic body radiation therapy (SBRT) is a promising therapy for patients with hepatocellular carcinoma (HCC). A radiopaque drug-eluting embolic bead used during TACE, called LC Bead LUMI (Boston Scientific), was developed to allow improved visualization during TACE. The purpose of this case series is to assess the visibility of LUMI after TACE and discuss its potential use as an alignment tool for SBRT.

Methods: Fourteen patients with HCC (median age 69) received TACE using LUMI immediately followed by SBRT to 50 Gy in 5 fractions (13 patients) or 40 Gy in 5 fractions (1). Computed tomography (CT) simulation and cone beam CT (CBCT) images taken before each fraction were compared with immediate post-TACE imaging. Success of the LUMI bead opacification was graded from excellent to poor visualization. Patients were followed to assess target lesion response, disease control, survival, and the long-term visibility of LUMI beads.

Results: CBCT immediately after TACE with LUMI displayed excellent tumor visibility for 6 of 13 patients (46.2%), moderate tumor visibility for 4 patients (30.8%), and poor tumor visibility for 3 patients (23.1%). When comparing CBCTs used for SBRT image verification to post-TACE CBCT, 53.8% remained unchanged and 46.2% deteriorated from excellent to moderate or moderate to poor, but none deteriorated from excellent to poor visualization. Median follow-up was 13 months (range 2-35). On average, LUMI beads were visible on noncontrast CT up to 20 months after SBRT.

Conclusions: LC Bead LUMI has the ability to provide liver tumor demarcation on noncontrast and cone beam CT weeks to months following TACE. It can serve as an alignment tool and could improve the therapeutic ratio in liver SBRT by allowing for tumor margin reduction with a potential decrease in the risk of toxicity when treating HCC in facilities without magnetic resonance imaging-linear accelerator.

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*Corresponding author: Emma C. Fields, MD; E-mail: emma.fields@vcuhealth.org

The incidence of hepatocellular carcinoma (HCC) has been significantly increasing over the last 30 years and has in fact doubled since 1980, with an estimated 43,230 new cases and 30,230 deaths predicted for 2021 in the United

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States.[1] As a result, treatment algorithms and technologies for HCC are rapidly evolving. The greatest challenge in this disease is to deliver aggressive treatment to the tumor while sparing the remainder of the liver, as there is typically underlying pathology and often cirrhosis.

The Child-Pugh classification is a widely used system that grades the severity of cirrhosis. It is incorporated in many treatment algorithms, including the Barcelona Clinic Liver Cancer (BCLC) staging classification, a largely accepted algorithm for the staging and management of HCC.[2] The Child-Pugh system uses bilirubin, albumin, prothrombin time, and the presence of ascites and/or encephalopathy to create a score that correlates with overall survival.[3] The BCLC classification of HCC creates 5 stages based on performance status, Child-Pugh classification, and HCC severity.[4] Generally, only patients with earlier stage BCLC disease are eligible for consideration of "curative" therapies such as resection, transplant, and thermal ablation. Unfortunately, about 70% of patients present with liver disease or tumors that are too advanced for these treatment options.[4,5] Therefore, other liver-directed treatment options have emerged to provide tumor control or palliation, or to downstage the tumor for transplant. Examples of these include transarterial chemoembolization (TACE), selective internal radiation therapy or Y-90, and more recently, stereotactic body radiation therapy (SBRT).

TACE is typically used for patients who are unsuitable for surgical or ablative treatments and has been shown to improve survival compared with best supportive care.[6] External beam radiation therapy has the advantage of being completely noninvasive; however, its use has been limited due to concerns for radiation-induced liver toxicity in this fragile population. Despite these concerns, several prospective trials have shown that SBRT is well tolerated and provides good local control and comparable rates of overall survival with TACE.[7-13] Theoretically, TACE and SBRT are an excellent combination for the treatment of unresectable HCC given the synergistic effects of chemotherapy and radiation. There is some interest in the combination of these modalities, and early nonrandomized data suggest a benefit compared with either modality alone in terms of local control and possibly overall survival.[14-16]

Over the years, conventional TACE has evolved to incorporate drug-eluting beads (DEBs) that provide an embolic effect in the nearby tumor vasculature while delivering focal chemotherapy. The use of DEBs sacrifices the long-term visualization of the tumor, which can be seen when using lipiodol-based techniques. A newer product has emerged that combines both concepts. LC Bead LUMI (Boston Scientific) is an intrinsically radiopaque embolizing bead, which can also be loaded with chemotherapy. This radiopaque attribute can provide direct intraprocedural and long-term visualization. Radiopaque material within the tumor weeks to months after TACE could provide radiation oncologists with an alignment technique for SBRT, allowing for bridging between treatment planning and setup.

The focus of this report is to describe 14 consecutive cases using TACE with radiopaque embolic beads (LC Bead LUMI) followed by SBRT in patients with unresectable HCC, and to describe the clinical utility of this combination for focal radiation therapy.

Materials and Methods

This study was approved by the institutional review board. A multidisciplinary hepatocellular tumor board discussed each case and arrived at the decision to treat each patient included in this report using TACE with radiopaque beads followed by SBRT based on clinical and imaging characteristics.

Before any treatment, all patients were consulted by both interventional radiology and radiation oncology and deemed appropriate candidates for combined therapy. All patients had TACE with LC Bead LUMI. LUMI bead vials contained 50 mg doxorubicin and a mixture of either 70 to 150 μm beads (6 patients) or 40 to 90 μm beads (8 patients). After the initial experience with the first 6 patients, the bead caliber was reduced to allow for improved distribution in the smaller tumor blood vessels and to decrease casting of the material in the larger vessels.

Cone beam computed tomograms (CBCTs) were obtained by the interventional radiology department within 1 hour of TACE to assess bead deposition. The date of TACE with LUMI bead placement was considered day 0 for all patients.

Postprocedure, patients were seen in radiation oncology for a computed tomogram (CT) simulation. All patients were simulated in the supine position with intravenous contrast and custom immobilization. Two patients were simulated and treated with breath-hold technique, while the other 12 patients had 4-dimensional CT scans to account for all phases of breathing and were treated in free-breathing. The use of the Active Breathing Coordinator system (Elekta) was discontinued at the start of the COVID-19 pandemic due to concerns of transmission risk.

Average visualization scores were calculated for post-TACE, CT simulation, SBRT CBCT using a 3-point scale, with 1 representing poor (<25% of the tumor with bead uptake), 2 representing moderate (25%-75% tumor uptake), and 3 representing excellent (>75% uptake) visualization based on the independent review of an interventional radiologist and radiation oncologist.

Target lesions were contoured based on coregistered diagnostic images as well as radiographic findings at the time of simulation. Planning target margins were customized based on setup and motion management with a goal

of <1 cm for each lesion. SBRT was planned according to Radiation Therapy Oncology Group protocol 1112 using a 5-fraction regimen with photons. The goal prescription was 50 Gy in 5 fractions and could be reduced by 5 Gy increments to respect the mean liver dose constraints. At least 48 hours were required between fractions to allow for normal tissue repair. Given this was a retrospective look at visibility of the LC LUMI Beads for SBRT tumor delineation and alignment, we did not adjust planning target volume (PTV) margins based on grade of visualization. All patients were planned and treated with a 5 mm margin from the internal target volume to the PTV. All patients were followed with clinical examinations, laboratory studies, and imaging every 3 months.

Results

Patient demographics

Fourteen patients (median age 69, range 54-82 years) were treated using TACE with LUMI followed by SBRT between November 2016 and January 2021. Of the 14 patients, 10 had hepatitis C as their primary liver disease and all were classified as Child-Pugh A. All patients had a single target lesion ranging from 1.5-5.6 cm in greatest dimension, and 3 patients had received prior treatments (Table 1).

Treatment information

LC Bead LUMI was delivered on day 0 for all patients. SBRT CT simulation for radiation planning was performed on day 12 on average (range 1-64 days) and SBRT was started on day 27 on average (range 12-83 days). Thirteen patients received 50 Gy in 5 fractions and 1 received 40 Gy in 5 fractions all over approximately 2 weeks, and the mean liver dose met constraints based on the Radiation Therapy Oncology Group protocol (Table 2).

Bead visualization

Following embolization with LC Bead LUMI, CBCT images were obtained within 1 hour. However, 1 patient did not receive volumetric post-TACE imaging, only plain films, and these were not used in the grading of LUMI uptake. Of the 13 other patients, 6 (46.2%) had excellent visibility of the LUMI beads, 4 (30.8%) had moderate visibility, and 3 (23.1%) had poor visibility of the beads in the region of the tumor (Fig 1).

Bead caliber was correlated with degree of visualization with only 1 patient of the first 6 using the larger diameter, who had excellent visibility (16.7%), whereas in the second 8 patients with the smaller bead caliber, 4 had excellent visibility (50%). Similarly, there were 2 patients in the large caliber group with poor visibility (33.3%) and only 1 in the smaller diameter group (12.5).

Between immediate post-TACE imaging and CT simulation, 84.6% remained unchanged, 15.4% deteriorated from excellent to moderate or moderate to poor, and none deteriorated from excellent to poor visualization.

In total, 28.6% of patients experienced bead visualization degradation between CT simulation and CBCT at the time of stereotactic radiation treatment. Between post-TACE CBCT and first SBRT, 53.8% remained unchanged, 46.2% deteriorated from excellent to moderate or moderate to poor, and none deteriorated from excellent to poor (Fig 2a). Overall, visualization was best post-TACE but decreased post-CT simulation and further decreased at post-SBRT CBCT (Fig 2b). Patients with 1 level of degradation of

Table 1

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10	Case 11	Case 12	Case 13	Case 14
Age	62	59	70	82	75	70	76	54	76	68	66	71	62	64
Sex	Male	Female	Male	Male	Male	Male	Male	Male	Male	Male	Male	Male	Male	Male
Primary liver disease	Hep C	Hep C	NAFLD	Hep C	Alcohol	Hep C	Hep C	Hep C, alcohol	Hep C	NAFLD, alcohol	Hep C	NAFLD	Hep C, alcohol	Hep C
UNOS stage	T4	T2	T2	T1a	T1a	T2	T4	T2	T3	T2	T1	T2	T2	T3
ECOG stage	0	0	1	2	1	0	2	0	0	0	0	0	0	0
Child-Pugh	A	A	A	A	A	A	A	A	A	A	A	A	A	A
BCLC stage	0	A	A	A	A	C	A	A	A	A	A	A	A	A
Number of lesions	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Target lesion size	2.1 cm	1.7 cm	3.4 cm	2.0 cm	1.5 cm	2.8 cm	3.5 cm	3.5 cm	3.0 cm	1.6 cm	1.6 cm	3.5 cm	2.6 cm	5.6 cm
Target lesion location	Right lobe (dome)	Caudate lobe	Right lobe	Right and Left lobes	Right lobe (dome)	Right lobe (dome)	Right lobe	Right lobe (dome)	Right lobe	Right lobe (dome)	Right lobe	Right lobe	Left lobe	Right lobe
Prior treatment	Microwave ablation, TACE × 3	None	None	None	None	Surgery, TACE × 2, microwave ablation, Y-90 × 2	None	None	TACE, microwave ablation	None	None	None	None	None

Abbreviations: BCLC = Barcelona Clinic Liver Cancer; ECOG = Eastern Cooperative Oncology Group; Hep C = hepatitis C; NAFLD = nonalcoholic fatty liver disease; TACE = transarterial chemoembolization; UNOS = United Network for Organ Sharing; Y-90 = yttrium-90.

Table 2

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10	Case 11	Case 12	Case 13	Case 14	Average ± Standard Deviation
CT simulation (days)	4	17	6	26	1	2	64	2	1	1	1	43	1	3	12.29 ± 19.36
SBRT start (days)	17	27	21	35	15	16	83	15	16	15	18	77	12	18	27.50 ± 23.03
SBRT completion (days)	28	37	33	47	24	27	93	26	30	28	33	90	22	31	39.21 ± 22.99
Dose to target (Gy)	50 Gy/ 5 fx	50 Gy/ 5 fx	50 Gy/ 5 fx	50 Gy/ 5 fx	50 Gy/ 5 fx	50 Gy/ 5 fx	40 Gy/ 5 fx	50 Gy/ 5 fx	50 Gy/ 5 fx	50 Gy/ 5 fx	50 Gy/ 5 fx	50 Gy/ 5 fx	50 Gy/ 5 fx	50 Gy/ 5 fx	
Mean liver dose (Gy)	2.45	10.17	12.86	6.21	6.32	12.98	14.19	6.57	2.25	6.37	11.15	11.68	9.86	8.74	8.70 ± 3.79

Abbreviations: CT = computed tomography; fx = fractions; SBRT = stereotactic body radiation therapy.

visibility had on average 34 days between post-TACE CBCT and start of radiation therapy (range 15-83 days).

Visualization of the LC Bead LUMI was not correlated with tumor location, prior treatment, or tumor size. Only 3 of the patients in this sample had received prior treatment, and 2 of the 3 had excellent visibility on post-TACE imaging. The patient who had received the most prior treatments had poor visibility and also had the larger caliber beads injected.

In this cohort of patients, 35.7% of lesions were located in the liver dome, which is challenging in regard to radiation therapy setup. However, in cases with excellent visibility, image verification with CBCT was very straightforward (Fig 3).

Treatment toxicity

Follow-up period for patients was determined from the end of SBRT to either the date of death or the last oncology clinic visit. The median follow-up of all patients was 13 months (range 2-35 months). No patient exhibited signs of acute toxicity, including liver toxicity, during treatment with LC Bead LUMI or SBRT.

Disease control

Follow-up abdominal magnetic resonance imaging scans confirmed local control in the target lesion for 10 patients at the latest follow-up. Fifty percent of patients developed disease in other sites of the liver, 16.7% developed metastatic disease, and 33.3% did not have progression or recurrence.

Target visibility

Noncontrast abdominal CT scans were available for cases 1, 2, and 3 long after treatment with TACE and SBRT. Bright, radiodense areas representing LUMI beads within the original target lesion were still visible on average 10.4 months (range 2-28 months) after SBRT for cases 1 and 3. LUMI beads were not visible on noncontrast abdominal CTs after treatment for case 2. This was expected because there was little to no visibility immediately after treatment.

Of note, 19 additional patients with HCC have been treated with TACE using LC Bead LUMI at our

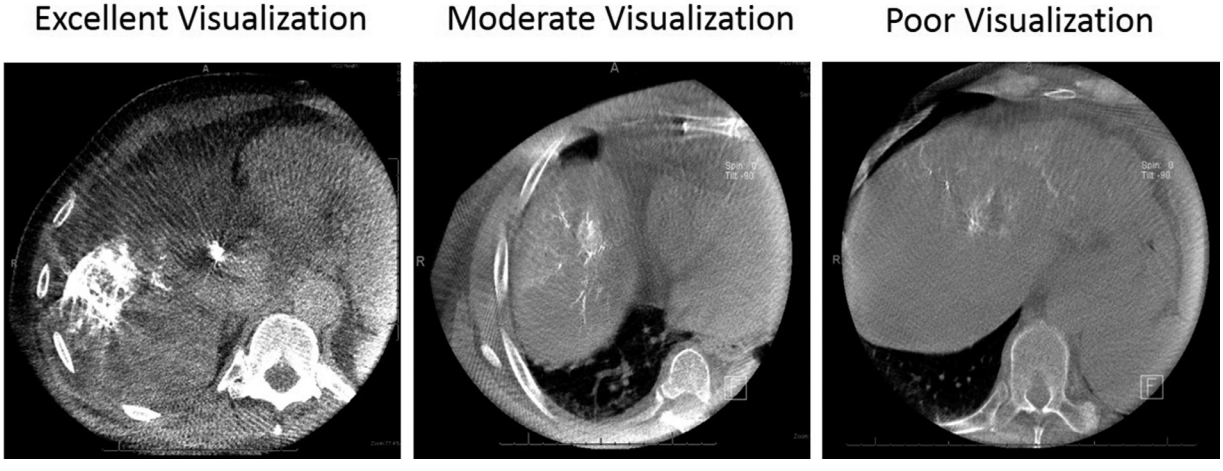

Figure 1 Initial post-TACE CBCTs showing an example each of excellent, moderate and poor visualization of LC Bead LUMI. *Abbreviations:* CBCT = cone beam computed tomography; TACE = transarterial chemoembolization.

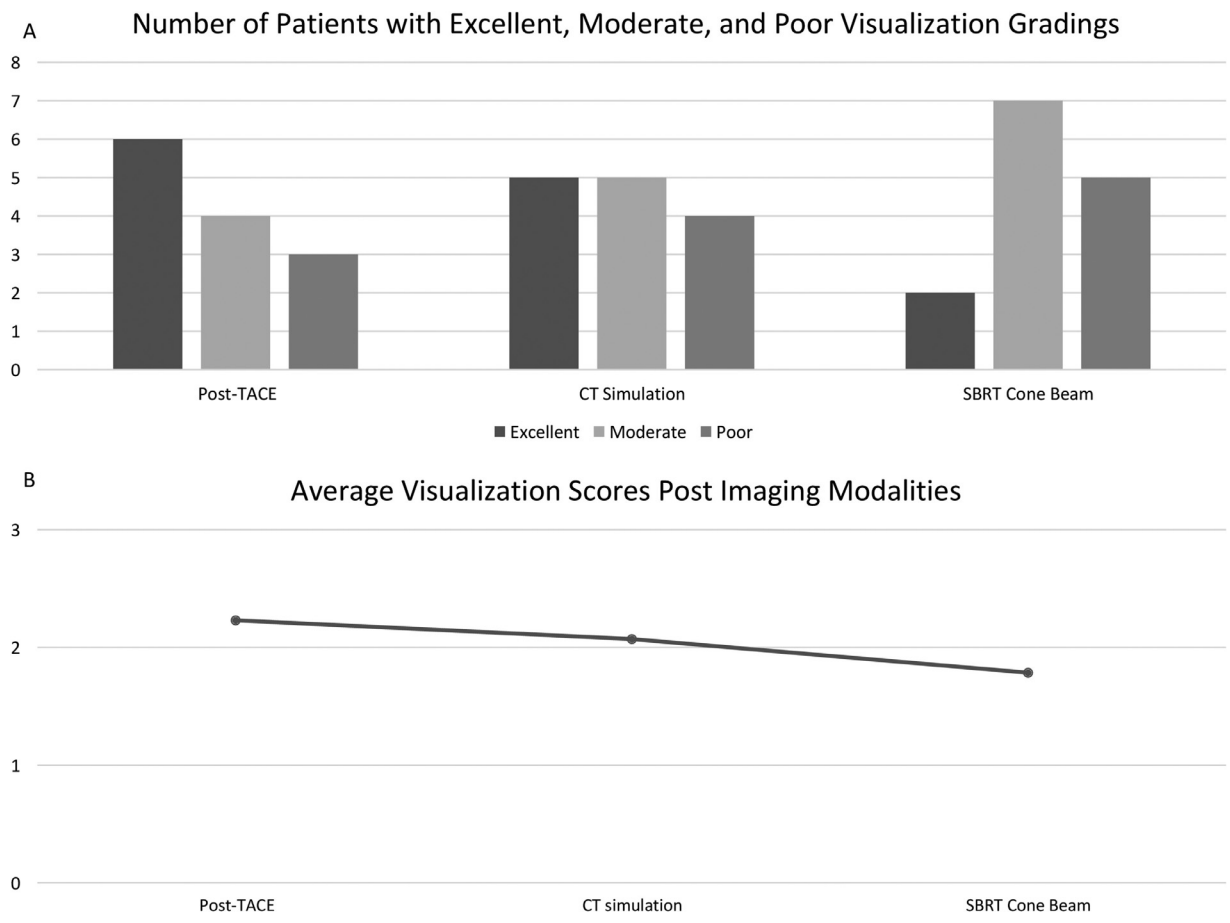

Figure 2 Graphical representation of visualization of LC Bead LUMI on SBRT alignment images (A) showing the number of patients with excellent, moderate and poor visualization at each timepoint and (B) showing the average visualization scores at each time point. *Abbreviations:* SBRT = stereotactic body radiation therapy.

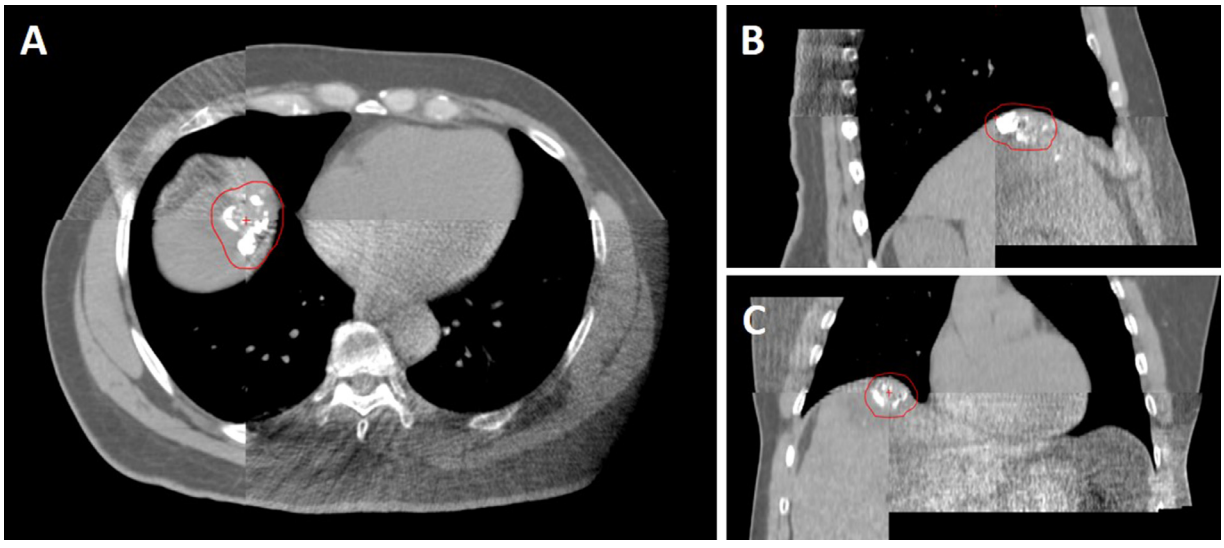

Figure 3 SBRT alignment CBCT showing setup of a liver dome lesion with excellent visualization of LC Bead LUMI. *Abbreviations:* CBCT = cone beam computed tomography; SBRT = stereotactic body radiation therapy.

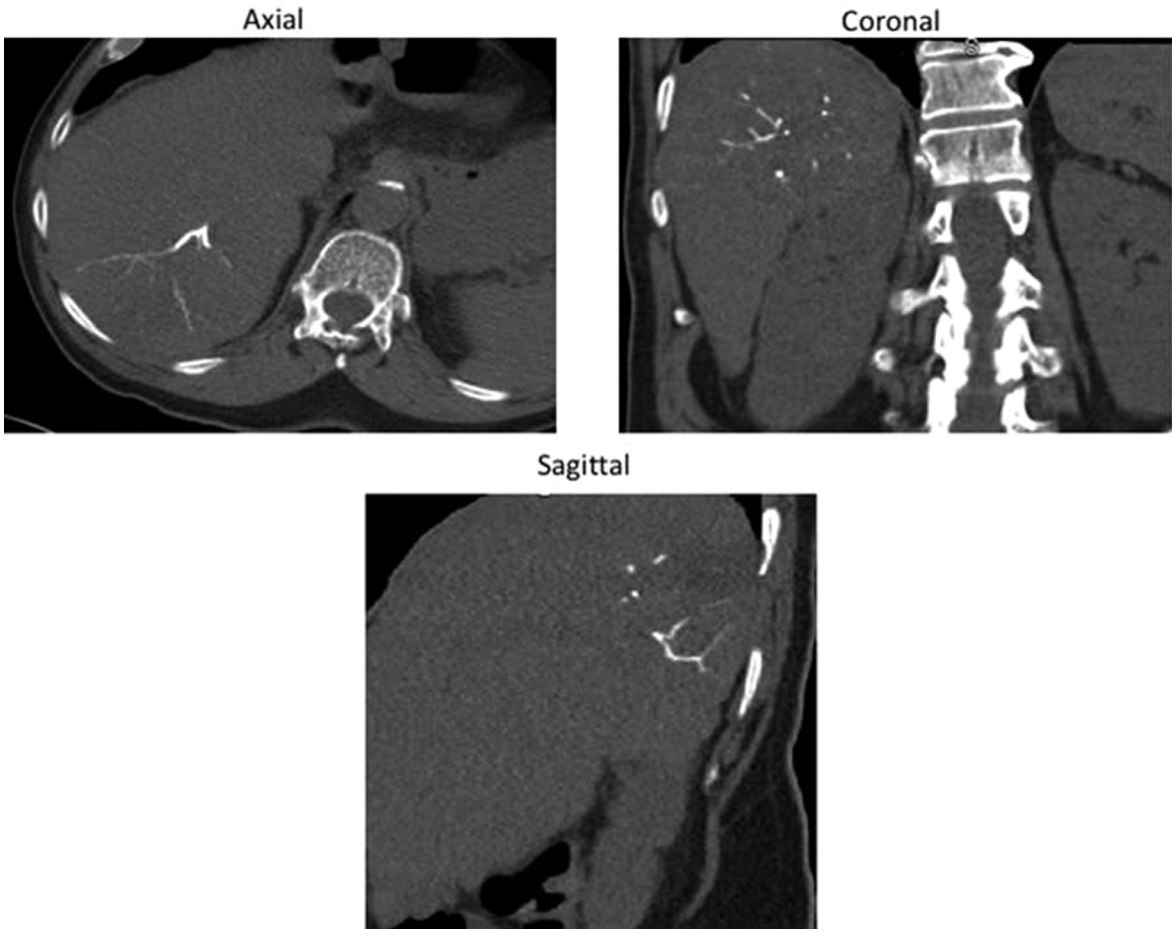

Figure 4 Noncontrast CT demonstrating a cast-like phenomenon after TACE with LC Bead LUMI. *Abbreviations:* CT = computed tomography; TACE = transarterial chemoembolization.

institution without the addition of radiation therapy. Some of these patients developed a cast-like material in some of the larger hepatic arteries after injection with LC Bead LUMI. An example of this is shown in Figure 4. This did not occur in any patients presented in this series, but is the reason for the change in caliber of the LUMI used partway through this experience.

Discussion

To our knowledge, this is the first clinical report demonstrating the combination of TACE with LC Bead LUMI followed by SBRT. We have demonstrated that when the radiopaque material has excellent visibility at 1-hour after the procedure, it either remains highly visible (83.3%) or degrades to moderately visible (16.7%). This indicates that if excellent visibility can be obtained at the time of TACE and LC LUMI Bead injection, then there is the highest likelihood of being able to use the markers for target delineation and image verification.

Conventional TACE involves a mixture of a radiopaque embolic liquid, lipiodol, often with liquid chemotherapy. Multiple chemotherapeutic agents have been used over the years, with doxorubicin being the most commonly used today. In this procedure, lipiodol is retained in hypervascular tumors and remains as a long-term radiopaque marker. It has the best efficacy in tumors with a good arterial blood supply and can result in long-term local control in patients with smaller tumors (less than 4-5 cm).[17] In the past decade, chemotherapy has been bound to beads for gradual drug elution, reducing the use of lipiodol with TACE. Though these DEBs are also retained in the tumor, they are not radiopaque, which sacrifices long-term visualization of the tumor.[18-20] LC Bead LUMI allows the increasingly common form of TACE, DEB-TACE, to become radiopaque.

With new technology allowing for more precision and image guidance, SBRT has shown high rates of local control and overall survival with low rates of liver toxicity.[12,21–24] The efficacy of TACE has increased when combined with other treatments such as SBRT or radiofrequency ablation.[22,25] Specifically, the combination of TACE and SBRT has improved rates of local recurrence and overall survival compared with TACE alone.[14-16] In a randomized study, median survival was 33 months in

the combined treatment group compared with 20 months in the group that received only TACE.[14] Huo and Eslick performed a systematic review and meta-analysis that showed increased overall survival that remained significant at 5 years when combining both treatment modalities.[26] More recently, a trial evaluating the feasibility of SBRT followed by TACE found this combination to be tolerable and found relatively high best overall response rate and clinical benefit observed in comparison to previous clinical trials with TACE alone.[27] Similarly, we show excellent rates of local control with this approach. Some theoretical reasons for this synergistic effect involve the distribution of vessels within the tumor. SBRT works best in the well-vascularized tumor periphery, whereas TACE tends to be more effective in areas with already compromised blood flow, further depriving these areas of adequate oxygenation. The known synergistic effects of concurrent chemotherapy and radiation in hepatobiliary malignancies may also contribute to this benefit.[28,29]

One of the major limitations in treating patients with HCC with SBRT is the risk of radiation-induced liver disease. The maximal dose that can be delivered to the tumor is limited by the liver's reserve or the tolerance of adjacent organs.[3] The patients presented in this case series demonstrate that it is possible to achieve excellent tumor demarcation used both for treatment planning as well as daily treatment setup. The improved localization could allow for a decrease in setup margins and thus less normal liver treated, leading to a decreased risk of radiation-induced liver toxicity.

Other localization techniques for the treatment of HCC with SBRT involve radiopaque agents such as lipiodol and fiducial markers. Properly placed fiducial markers allow for excellent targeting of liver tumors and for reduced margins when intrafraction tracking or gating is used.[30,31] However, tumor location and ultrasonographic visibility can make proper marker placement difficult, particularly in locations such as the liver dome.[32] The placement of traditional fiducial markers also requires the patient to undergo an invasive procedure with its own theoretical risks and only the potential benefit of improved day-to day setup. With the LC Bead LUMI TACE patients have an additional procedure, but it has the potential benefit of adding combined modality treatment.

Although the beads provided improved visualization in most patients, it was not seen in all of our patients. There is an intrinsic limitation to the technique that occasionally occurs if there is difficult vascular anatomy, as demonstrated in case 2. In this case, the feeding artery was too small for microcatheterization, making the treatment zone and correlating dose suboptimal. In comparison to our results, a recent single institutional prospective observational cohort study including 44 patients with either BCLC stage A or B disease showed high rates of tumor visibility at 1 hour after the procedure on noncontrast CT.[33] Most patients (57%) displayed 75% to 100% target nodule involvement, 23% displayed 25% to 75% uptake, 16% displayed less than 25%, and a collection of beads was noted in the cholecystic wall in 2 patients (5%).

Another limitation is the splay of cast-like material, which has been seen in larger hepatic arteries such as in case 5. At present, the lesion appears to be adequately treated, but this may prevent further intra-arterial treatment. There are no data to support increased toxicity when cast-like material builds up postprocedurally. The lack of toxicity may be due to the persistent perfusion of liver tissue by the portal venous system.

Similarly, there is a deterioration in visibility of the beads seen over time. In this cohort, we found that 28.6% of patients had degradation in visibility between CT simulation and SBRT, with an average interval of 27.5 days. Given the long delay some patients experienced, it would be prudent to minimize the time interval if the beads are planned to be used for target delineation and patient setup.

To our knowledge, there are no studies in this patient population evaluating the long-term visibility of LC Bead LUMI. For patients presented in this case series with adequate follow-up imaging, LUMI beads continue to be visible on noncontrast CT many months after treatment. In an animal model, 1 study did show clear visualization without deterioration on CT at 7, 14, 30, and 90 days.[34] It is not known how the presence of the beads affects surveillance scans after SBRT. This is an interesting area for future investigation.

Conclusions

TACE and SBRT have the potential to escalate the efficacy of our treatment for HCC compared with TACE or SBRT alone. LC Bead LUMI is an intrinsically radiopaque drug-eluting embolic bead used with TACE that is capable of providing tumor demarcation on noncontrast and cone beam CT weeks to months after TACE. This technique has the potential to benefit patients by omitting the need for a separate fiducial marker placement, reducing PTV margins, and allowing SBRT to be combined with TACE. The extent of tumor demarcation and clinical utility of this technique should be evaluated in a larger number of patients.

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