RESEARCH ARTICLE

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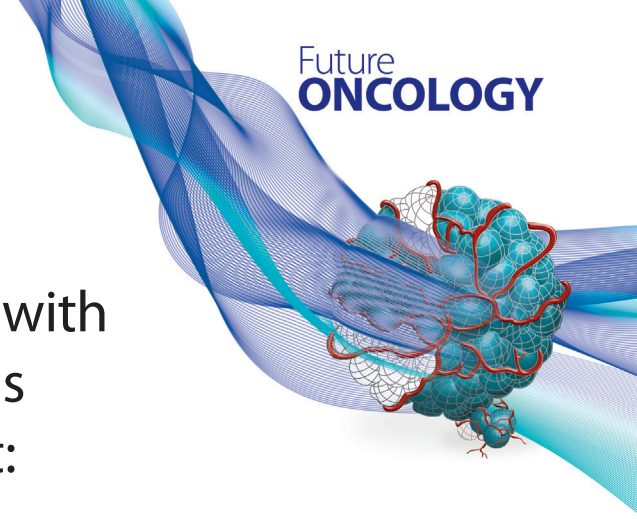

Transarterial chemoembolization with DC Bead LUMI™ radiopaque beads for primary liver cancer treatment: preliminary experience

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Aim: Primary objectives of the study were to assess the safety of transarterial chemoembolization (TACE) using DC Bead LUMI™ for the treatment of hepatocellular carcinoma and beads distribution after TACE. **Patients/methods:** This was a prospective observational cohort study. The study included 44 hepatocellular carcinoma patients who were treated with TACE using DC Bead LUMI. Beads distribution was monitored 1 h after TACE by CT scan. **Results:** TACE had no intraprocedural complications. Observed side effects were of mild intensity and included pain in 5 (11%), fever in 4 (9%) and vomiting in 2 (5%) patients. Most patients (89%) reported no adverse event. Non-target distribution was observed in only two cases (5%). **Conclusion:** DC Bead LUMI allowed assessing in real time their distribution. This could prevent non-target infusion and reduce toxicity.

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KEYWORDS: arterially directed embolic therapy • chemoembolization • DC Bead LUMI radiopaque beads • hepatocellular carcinoma • TACE

Transarterial chemoembolization (TACE) belongs to the arterially directed embolic therapies (ADET) and is a widely used loco-regional therapy for the treatment of advanced or unresectable hepatocellular carcinoma (HCC) [1]. HCC vascularization is mainly supplied by the hepatic artery. Catheterization of the local hepatic artery can allow tumor visualization by angiography and injection of embolic agents (loaded with cytotoxic drug or radioisotopes). TACE can block tumor vascular supply, enable delivery of cytotoxic agents or radiotherapy to the tumor site and hence reduce disease progression [2]. There are several advantages of TACE: slow drug elution, reduced liver and systemic toxicity, increased local drug concentration, and tissue necrosis [3,4].

Doxorubicin administration with TACE improves survival and tumor response, resulting in a significant number of complete response and prolongs progression-free survival in HCC [5].

TACE can be applied as neoadjuvant therapy, bridge to surgery and palliative care to prolong survival for HCC. Recent TACE improvements include the introduction of new types of microspheres [4–7]. They offered a greater possibility of treatment for HCC, even if DC beads did not improve overall survival as compared with conventional TACE (cTACE), as reported by Precision Italia and other studies [8–11].

DC Bead LUMI™ is among the new types of embolic agent that have recently been introduced in EU. They are precisely calibrated and radiopaque microspheres that can be loaded with

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a chemotherapeutic drug. DC Bead LUMI contains a covalently bound radiopaque moiety that confers inherent and lasting radiopacity. They are visible under imaging modalities such as computed tomography (CT) and cone beam CT (CBCT) [12–15]. The advantage of DC Bead LUMI is that they can be visualized in real time during TACE and in follow-up imaging.

This allows the interventional radiologist to have intraprocedural feedback on the spatial localization of the beads and on the local drug delivery. On experimental evidence, this indicates where the eluted drug is likely to be at the highest concentrations [12–14].

Primary objectives of this observational prospective cohort study were to assess the safety of chemoembolization using DC Bead LUMI for the treatment of HCC and beads distribution after TACE. Secondary objectives were to identify lesions non-adequately treated or large lesions (>3 cm) partially treated that required a second TACE and to avoid over treatment.

In this paper we report the preliminary results of DC Bead LUMI use in TACE for the treatment of HCC, showing data on safety and bead distribution.

Materials & methods

• Characteristics of sample population

This is a prospective single-center observational cohort study on the use of DC Bead LUMI in clinical practice for the treatment of primary liver cancer. The study was reviewed and approved by the Azienda Ospedaliera 'Ospedali Riuniti Marche Nord' Institutional Review Board and was part of the study (Clinicaltrials.gov Identifier no. NCT01891539). Every patient signed the informed consent before enrollment.

We selected patients who were indicated for TACE due to unresectable HCC and performed TACE using DC Bead LUMI loaded with doxorubicin from March 2017 to May 2017. We evaluated beads distribution both intra- and post-procedurally and monitored adverse events.

We included 44 eligible consecutive patients that responded to the following criteria: older than 18 years; informed consent signed; diagnosed with HCC unilobar or bilobar; indication for TACE; performance status (PS) less than two; tumor dimension measurable with RECIST version 1.1 [16]; liver involvement less than 50%; liver function allowing TACE; BCLC stage A or B, platelets (PTL) not inferior to 60.000; and life expectancy greater than 3 months.

Patients were excluded if they were not indicated for angiographic catheterization and occlusion procedures, had extra-hepatic cancer, portal vein thrombosis (PVT), severe comorbidities, or were intolerant to doxorubicin and contrast medium.

• Protocol of arterially directed embolic therapy

The procedure for TACE has been previously described [6,7]. A diagnostic angiography was performed before the procedure in order to assess tumor arterial perfusion. Extra-hepatic embolization was avoided by using distal catheterization.

TACE was performed by infusing one vial (2 ml) of DC Bead LUMI (Biocompatibles UK Ltd, Farnham, UK, a BTG group company) loaded with 50 mg of doxorubicin. The diameter of the microspheres was 70–150 micron. We initially used a 100% dilution which was performed with 18 ml of contrast medium (Omnipaque 350, GE Healthcare srl, Little Chalfton, UK) that were added to 2 ml of DC Bead LUMI. We observed that this dilution resulted in increased suspension stability of the beads. However, the resulting viscosity of the solution was high with consequent greater infusion difficulties. The high viscosity of the undiluted solution resulted in a reduction of the volume of the beads that could be infused.

For this reason we used a 50% dilution that allowed an adequate suspension time, no aggregate formation and lower solution viscosity, requiring careful management to avoid settling of beads in the syringe and potentially blocking the catheter. Median of the delivered dose with 100% dilution was 0.40 ml, while with the 50% dilution was 1.45 ml. The 50% dilution was performed with 9 ml of contrast medium (Omnipaque 350) that were added to 2 ml of DC Bead LUMI and 9 ml of physiologocal saline solution. The settling in the 50% dilution was more evident than undiluted solution, but it was sufficient to shake the syringe to maintain an adequate suspension.

The catheter used for the infusion was 2, 7 French (Progreat, Terumo Europe NV, Leuven, Belgium). Administration was selective or super selective in each case. The injection style used was small puffs at a fixed rate of 1 ml/min.

Periprocedural and supportive therapy for adverse events prevention consisted of intravenous administration of 4 mg of ondansetron, one

vial of 4 mg omeprazol and one vial of 10 mg of morphine. Intra-arterial injection of 3 ml of lidocaine chlorhydrate (10 mg/ml) and 2.5 mg of verapamil was also performed. Post-TACE support therapy included morphine, ondansetron, ciprofloxacin and paracetamol in case of fever.

• Beads distribution

A CT scan was performed 1 h after TACE in order to monitor beads mapping **(Figures 1–3)**. Target lesion distribution was observed in all patients (100%). However beads were not evenly distributed inside the target lesion in all cases.

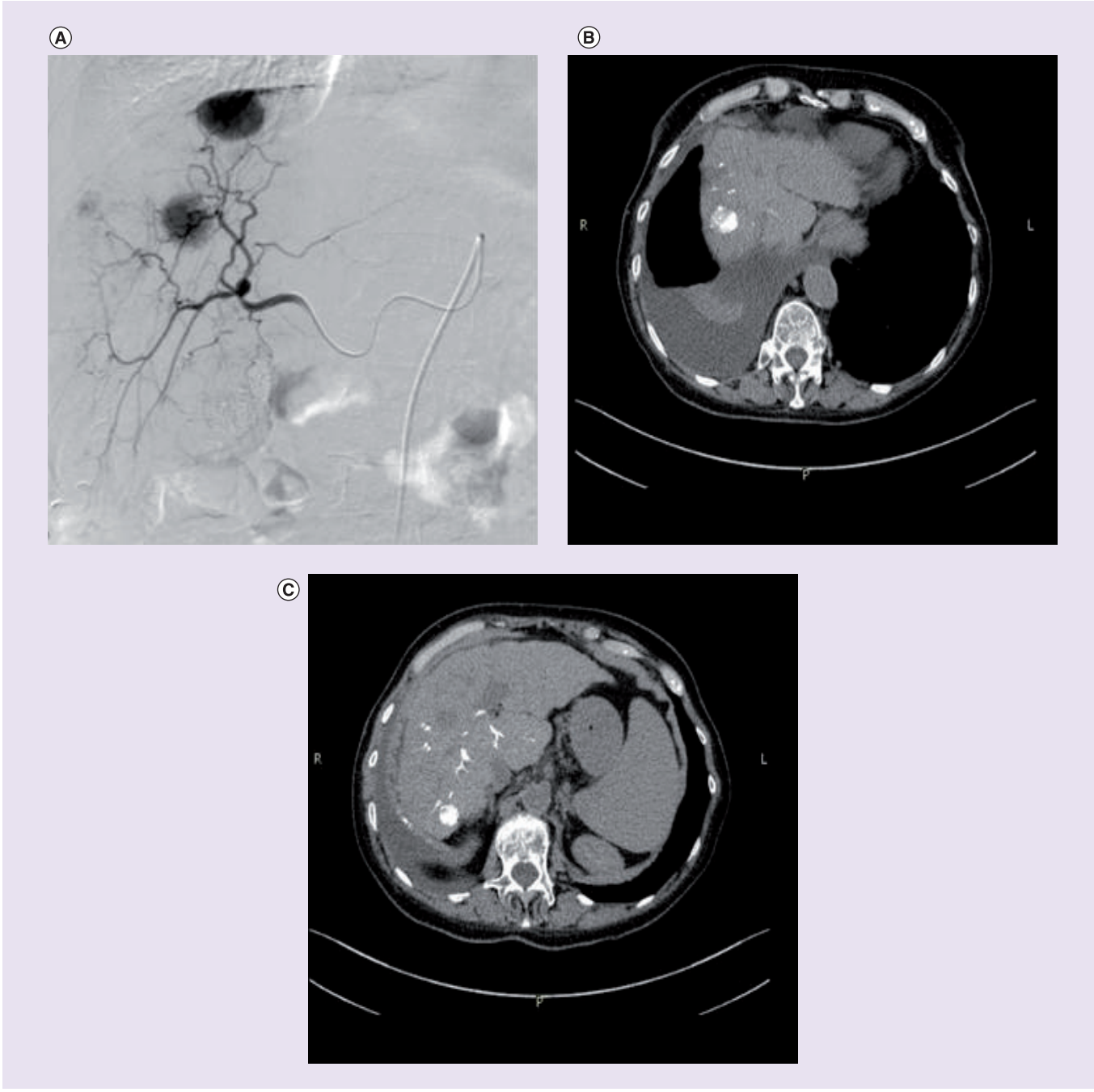

Figure 1. Transarterial chemoembolization with DC Bead LUMI™ in hepatocellular carcinoma, case one. (A) Intraprocedural angiography that shows a multifocal hepatocellular carcinoma with two target nodules, one in the hepatic cupola and one in the VII liver segment **(B)** CT scan 1 h after transarterial chemoembolization with G1 distribution of DC Bead LUMI inside hepatic cupola. **(C)** CT scan 1 h after transarterial chemoembolization with G1 distribution of radiopaque beads inside VII liver segment.

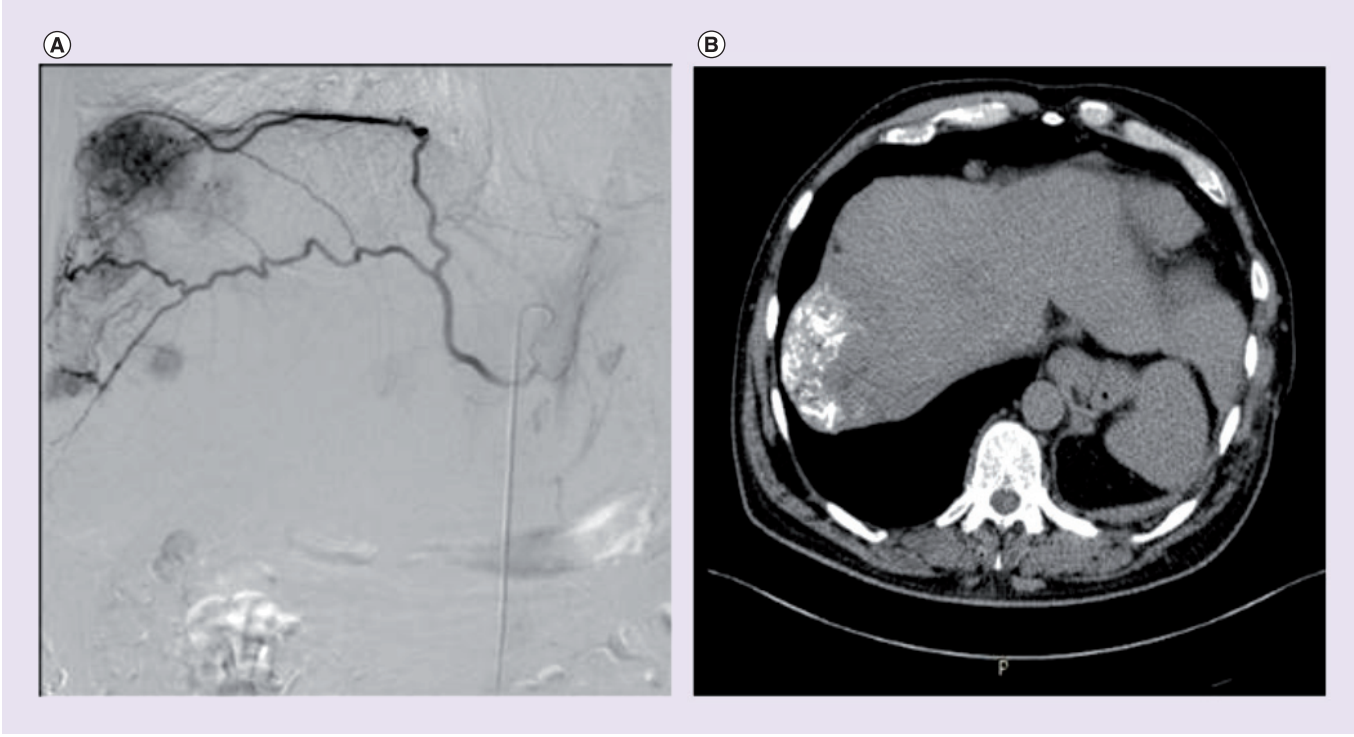

Figure 2. Transarterial chemoembolization with DC Bead LUMI™ in hepatocellular carcinoma, case two. (A) Intraprocedural angiography that shows a multifocal hepatocellular carcinoma with one voluminous target nodule in the hepatic cupola. **(B)** CT scan 1 h after transarterial chemoembolization with a G2 distribution of DC Bead LUMI inside hepatic cupola.

Distribution of DC Bead LUMI was classified according to the percentage of target nodule involvement: G1 was 75–100% of target nodule, G2 was 50 ± 25% of target nodule, G3 was <25% of target nodule and G4 corresponded to non-target localization of the beads **(Figure 4)**.

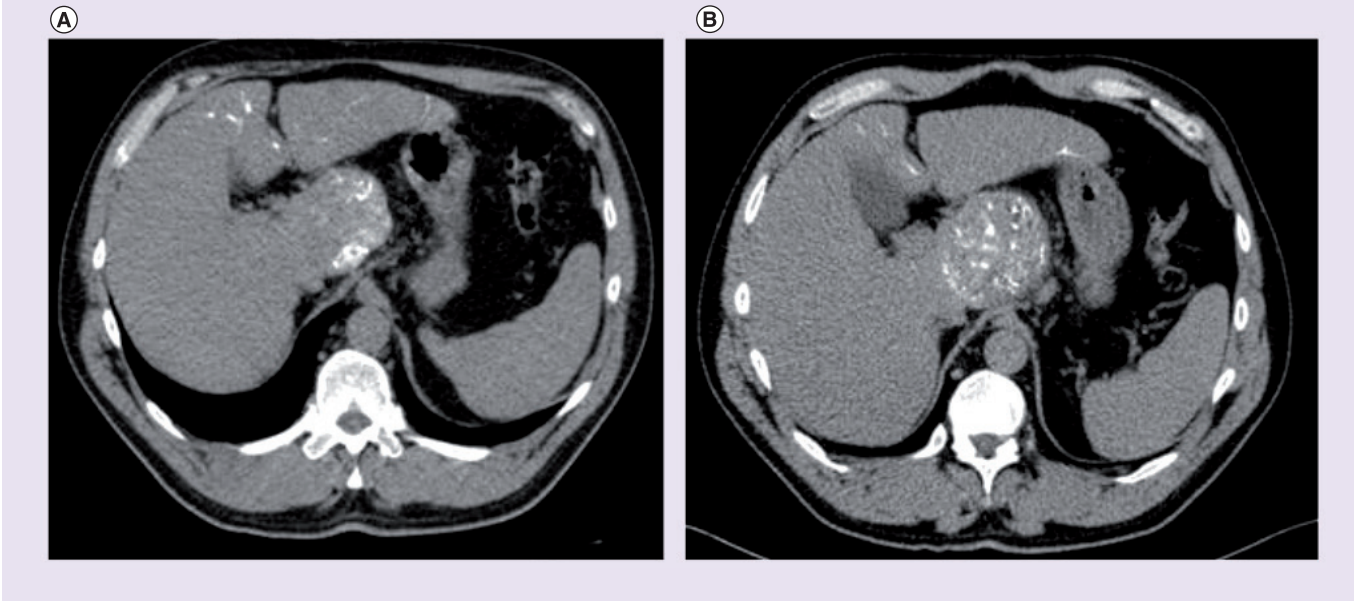

Figure 3. Treatment of large volume nodule. A large nodule in S1 was treated twice with transarterial chemoembolization: **(A)** First treatment in half of the nodule, **(B)** second treatment in the remaining half of the nodule.

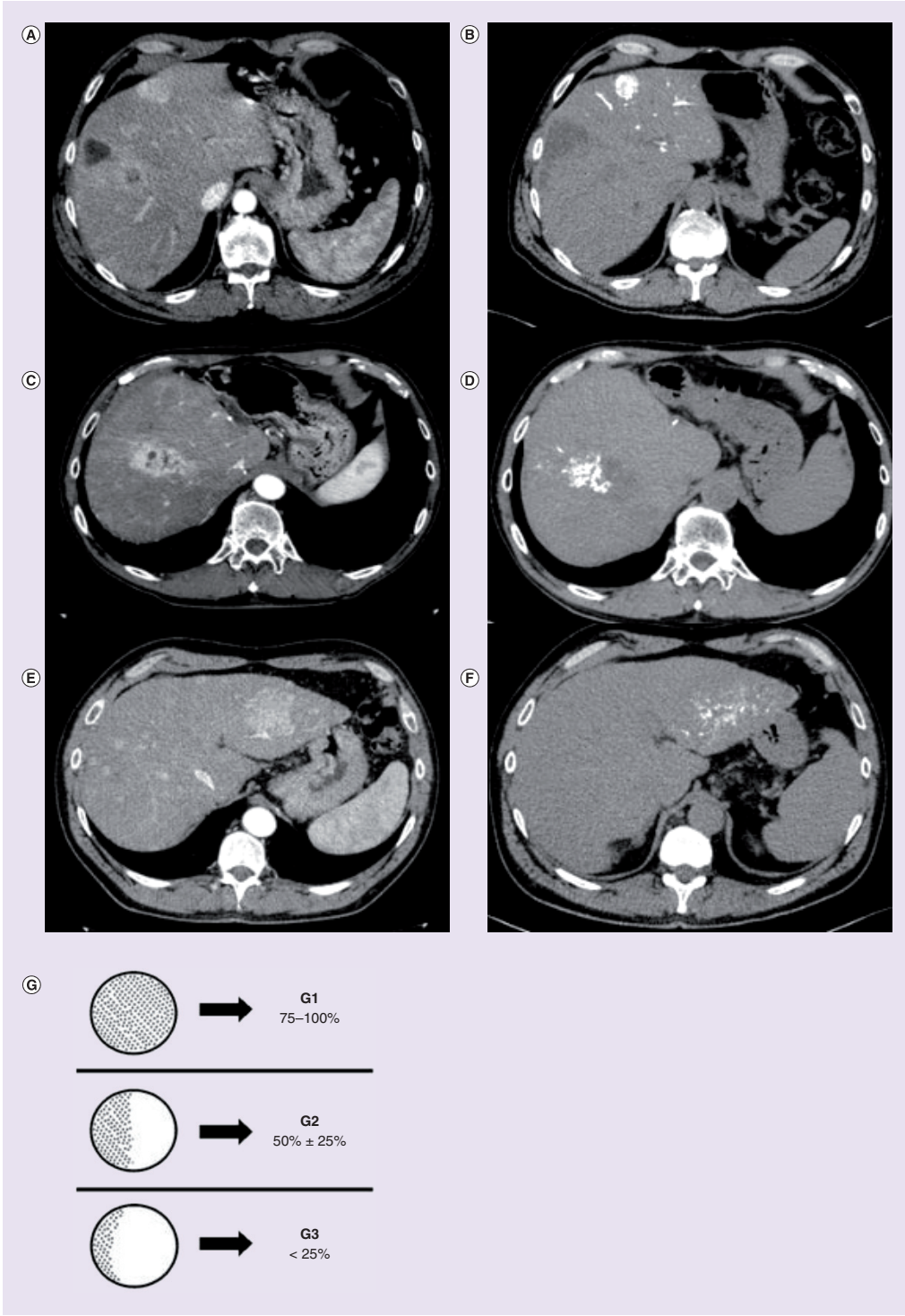

Figure 4. Classification of beads distribution 1 h post transarterial chemoembolization.
(A, C & E) CT scan of pretreatment nodules with contrast medium, **(B)** 1 h post transarterial chemoembolization, Grade 1 = distribution of the beads in 75–100% of the volume of target nodule; **(D)** 1 h post transarterial chemoembolization, Grade 2 = distribution of the beads in 50 ± 25% of the volume of target nodule; **(F)** 1 h post transarterial chemoembolization, Grade 3 = distribution of the beads in <25% of the volume of target nodule; **(G)** Schematic illustration of post-treatment beads distribution.

• Tolerability

Type and intensity of adverse events were evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.03.

• Statistical analysis

Descriptive data analysis was performed on the whole sample (n = 44). Continuous data were reported as median and range. Proportions were reported in percentage. Chi-square and Student's *t*-test were used to assess significance of continuous variables ($p < 0.05$).

Results

• Patients' characteristics

The study included 44 patients with HCC who were treated with TACE using DC Beads LUMI from the first of March 2017 to the end of May 2017. The majority of patients had 1–2 or 2–3 nodules (66 and 20% respectively); median nodule size was 27 mm (range 8–75 mm). As concerning liver involvement 36 (82%) were unilobar and 8 (18%) bilobar **(Table 1)**.

The patient population consisted of 36 (82%) males and eight (18%) females. Median age of the patients treated was 66 years (range 49–86). Previous surgery was performed in 22 (50%) patients. Previous systemic therapy (mainly sorafenib) and locoregional therapy were administered to 13 (30%) and 18 (41%) patients respectively.

Table 1. The patients' demographics.

	n	%
Median age years (range)	66	(49–86)
Female	8	18
Males	36	82
Number of nodules 1–2	29	66
Number of nodules 3–4	9	20
Number of nodules> 5	6	14
Nodules size mm (range)	27	(8–75)
Unilobar	36	82
Bilobar	8	18
Previous surgery	22	50
No previous surgery	22	50
Previous chemotherapy	13	30
Previous locoregional therapy	18	41
No previous chemotherapy	21	48
Drug dilution 50%	33	75
Drug dilution 100%	11	25
Median volume of infused beads ml (range)	1, 4	(0, 3–1, 8)

Previous loco-regional therapy were administered to 18 (41%) patients. At the time of the data analysis most patients (95%) received one TACE **(Figures 1 & 2)**, whereas two (5%) patients received two TACEs following a partial response after the first treatment. One of these patients had a voluminous nodule in S1. The first TACE with DC Bead LUMI enabled the confirmation of treatment in half of the nodule. The second TACE was performed 2 weeks later and targeted the remaining half of the nodule **(Figure 3)**. The use of DC-Beads LUMI allowed visualization of the part of the nodule that was not completely treated in the first TACE and planning for a second TACE.

We initially used 100% contrast to dilute DC Bead LUMI in 11 (25%) patients. Then, we adopted a 50% dilution of the infusing solution to reduce the solution viscosity for the remaining 33 patients (75%).

CT scan at 1 h after TACE showed beads distribution was G1 (75–100% of target nodule) or G2 (50 ± 25% of target nodule) in the majority of patients: 25 (57%) and 10 (23%) respectively. G3 (<25% of target nodule) distribution of the beads was observed in seven (16%) cases. Non-target localization of the beads in the cholecystic wall was observed in two (5%) patients **(Table 2)**.

The differential beads distribution might be due to nodule vascularization or wrong artery selection. Nodules with a good vascularization allowed G1 and G2 distributions due to high concentration of beads and hence high visibility in imaging. Nodules with a lower concentration of beads were less visible in the CT scan, showing a G3 distribution in seven cases.

The advantage of knowing the beads distribution enabled the physician to verify if the nodule treatment was already complete 1 h and not 1 month after TACE. For this reason, a second TACE could be performed earlier to treat the partially treated or untreated nodules. This was performed in two patients (5%), and the second procedure was performed 2 weeks after the first, instead of 4 weeks as in usual practice.

Non-target localization of DC Bead LUMI inside the cholecystic wall was identified 1 h post TACE in two cases. This might be due to abnormal vascularization **(Figure 5)**. The early detection of non-target beads distribution 1 h after TACE allowed the prompt treatment of potential side effects such as cholecystitis or pancreatitis that were not observed at the 1 month follow up control visit. These patients were strictly monitored

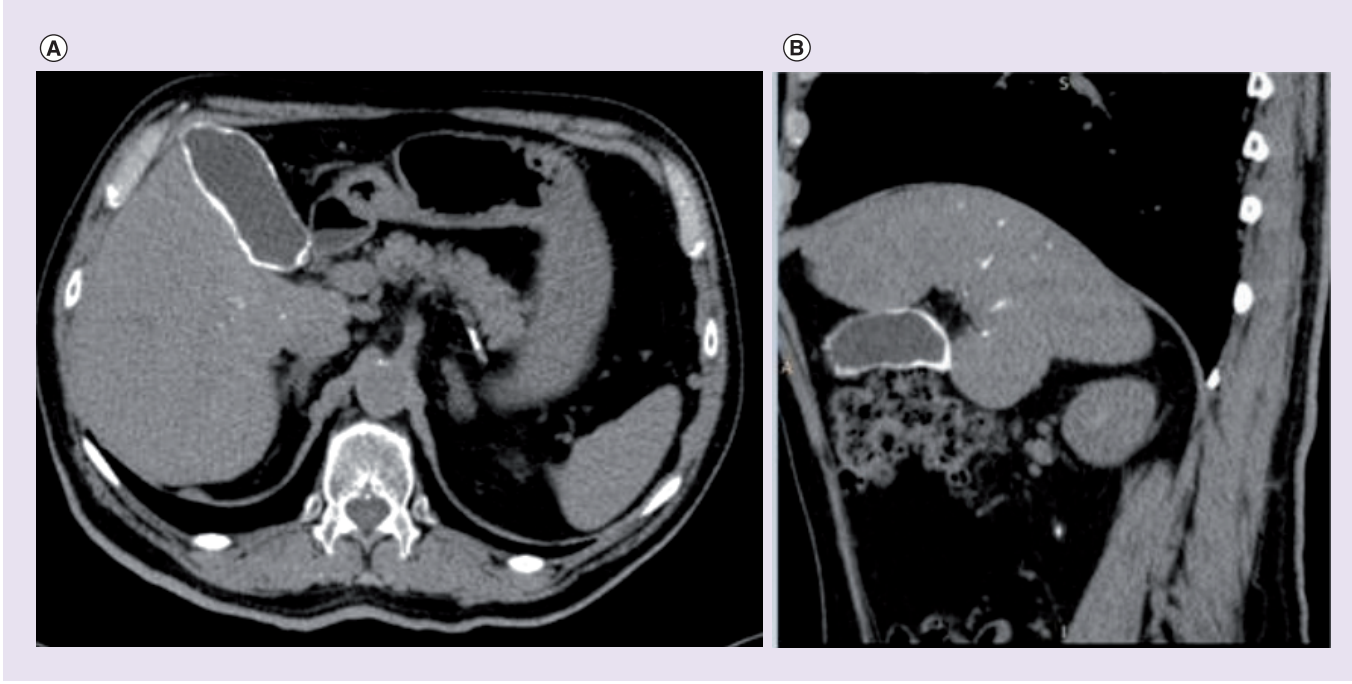

Figure 5. Non-target distribution. Beads were not distributed in the target nodule but in the in the cholecystic wall: **(A)** axial plane, **(B)** sagittal plane.

and were administered support therapy (antibiotics and anti-inflammatories, NSAIDS) and no cholecystitis was observed.

• Tolerability

TACE was performed without intraprocedural complications. Periprocedural and supportive therapy for adverse events prevention was provided according to our standard protocol [6,7]. Observed side effects were of mild (G1) intensity and included: pain in five (11%); fever in four (9%); and vomiting in two (5%) patients. Most patients (89%) did not complain of any adverse event **(Table 3)**. Hospitalization was 24–48 h.

Discussion

The results of this study on HCC treatment with TACE using DC Bead LUMI showed that monitoring beads distribution 1 h after TACE was significant to determine whether or not they had reached the target nodule(s). This allowed a second TACE to be performed earlier to treat the remaining portion of nodule or other nodules that were not reached with the first treatment. The physician did not need to wait for the control CT scan 1 month after TACE to know tumor response and schedule further treatments.

The early identification of non-target bead localization also helped to avoid and reduce adverse events and their clinical manifestation. Non-target localization of DC Bead LUMI inside the cholecystic wall was identified 1 h post TACE in two cases. These patients were strictly monitored and received supportive therapy to prevent cholecystitis, which was avoided in both cases. We noted that limited distribution of beads in the cholecystic wall did not always result in pain during and after the procedure. This has never been reported in the literature.

HCC are among the most difficult cancers to treat with very few surgical and therapeutic choices [1,17]. They are very frequent and are the leading cause of hundred thousand cancer deaths worldwide [18,19]. Unresectable primary liver

Table 2. DC-Bead LUMI™ distribution.

Correspondence between target and LUMI distribution	n	%
Yes	42	95
No	2	5
Non-target LUMI distribution 1 h after TACE		
Yes	2	5
No	42	95
G1 (75–100%)	25	57
G2 (50 ± 25%)	10	23
G3 (<25%)	7	16
G4 (non-target)	2	5

Table 3. Adverse events.

Adverse events	n	%
Pain (G1)	5	11
Fever (G1)	4	9
Vomiting (G1)	2	5
None	39	89

cancers are indicated for locoregional treatments, such as TACE, transarterial radioembolization (TARE) and ablative methods [6].

The use of TACE has greatly increased in the last 5 years, especially with the introduction of new types of beads such as spherical polyvinyl alcohol (DC Bead™) and DC Bead LUMI.

The opacity of DC Bead LUMI is not like that of the lipiodol [20], it remains in the vessel and does not interfere with the contrast medium CT scan to monitor the presence of residual tumor or progression of disease.

1 h post TACE with DC Bead LUMI, the CT scan also allowed the physician to identify incomplete or partial treatment of the nodule. In this situation, it was possible to immediately plan the next treatment and assess which vessels required treatment at the subsequent TACE to target the undertreated area of the nodule. This was performed in two patients (5%) and the second procedure was performed 2 weeks after the first, instead of 4 weeks as in usual practice.

Tolerability analysis showed that the most common adverse events were pain in five (11%), fever in four (9%) and vomiting in two (5%) patients. Most patients (89%) did not complain of any adverse event. The toxicity profile was lower than that observed with other types of beads [4–8]. Pain might be less than that reported in studies on TACE with other beads, where pain was 25–30% [6–8,21]. Another important aspect of our experience with DC Bead LUMI was the observation that beads suspended in 100% contrast agent resulted in their increased suspension stability as in previous reports [22–24]. In this case, however, the resulting viscosity of the solution was high with consequent greater infusion difficulty and possible reduction of the volume of beads that could be infused.

For this reason we adopted a 50% dilution of the infusing solution as reported in the methods section. This resulted in a reduction in solution viscosity and reduced suspension time requiring careful management to avoid settling of beads in the syringe and potentially blocking the catheter. This allowed a better infusion and greater volume of infused beads.

Principal limitations of this report are the limited number of patients enrolled the short period of observation. DC Bead LUMI is a new product and further studies are required to monitor long-term tumor response, survival and tolerability in a larger number of patients.

These results, however, are interesting because this is the first report on the application in every day clinical practice of DC Bead LUMI loaded with doxorubicin in patients with unresectable HCC.

A significant advantage of DC Bead LUMI is their direct visualization during the procedure, which allows the interventional radiologist to verify the correct placement of the beads close to the tumor and to identify any areas of under treatment for subsequent therapy. In the future it may be able to correlate radiopacity with drug levels and have an approximate measure of local drug concentration in the embolized territory [25].

Conclusion

TACE with DC Bead LUMI loaded with doxorubicin is a new step forward in the chemoembolization field, for the treatment of primary liver cancer.

The main advantage of DC Bead LUMI was knowing in real time their distribution. This enabled the mapping of tumor and non-target localization of the beads. This aspect permits a better management of the patient, preventing side effects due to this non-target localization.

Future perspective

Patients with HCC are often unresectable and indicated for locoregional therapy. TACE is among the most used locoregional method. DC Bead LUMI is a new type of embolics that can be visualized and have been recently launched in the EU.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

SUMMARY POINTS

- DC Bead LUMI™ radiopaque beads are drug-eluting beads that incorporate iodine and are visible in real time CT scan.
- Distribution of DC Bead LUMI was G1 (75–100% of target nodule) or G2 (50 ± 25% of target nodule) in the majority of patients 25 (57%) and 10 (23%) respectively.
- G3 (<25% of target nodule) distribution of the beads was observed in seven (16%) cases.
- Non-target localization of the beads in the cholecystic wall was observed in two (5%) patients. These patients were strictly monitored and were administered supportive therapy and no severe cholecystitis was observed.
- The treatment of primary liver cancer with transarterial chemoembolization using DC Bead LUMI resulted in low levels of toxicity.
- Toxicity was lower than that of other non-radiopaque beads.
- The main DC Bead LUMI advantage is knowing in real time their distribution.
- This allows the interventional radiologist to identify the localization of beads in real time, identify non-target localization and prevent the related side effects.
- Transarterial chemoembolization with DC Bead LUMI loaded with doxorubicin can be a new step forward in the chemoembolization field, for the treatment of primary liver cancer.

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