# Hepatic Arterial Infusion of Polyethylene Glycol Drug-eluting Beads for Primary and Metastatic Liver Cancer Therapy

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**Abstract.** *Background/Aim: Recently, there has been the launch of the new Polyethylene glycol (PEG) drug-eluting beads (LifePearl®) for transarterial chemoembolization. Their innovation is that PEG guarantees more compressibility, elasticity and maximizes beads' suspension time. We applied these beads for hepatic intra-arterial infusion of irinotecan or doxorubicin for the therapy of primary and metastatic liver cancer. Patients and Methods: We treated 20 consecutive patients, affected by unresectable primary liver cancer (PLC) or hepatic metastases (refractory to chemotherapy) using chemoembolization with doxorubicin or irinotecan pre-loaded Lifepearls. Results: Tumor response rate was >80% in most patients with 63% of complete and 37% of partial response. We observed no complications during the chemoembolization and no severe general drug-related side-effects. Conclusion: Our data suggest that chemoembolization with LifePearl® is efficacious and safe for the treatment of liver cancer as indicated by good tolerability, quality of life and high tumor response.*

Trans-arterial chemoembolization (TACE) is the most used treatment for patients with unresectable hepatocellular carcinoma (HCC) because it improves median survival and tumor response (1). The application of drug-eluting beads to this procedure has significantly increased TACE efficacy, while reducing systemic drug leakage, liver toxicity and adverse events (1). These beads deliver the toxic drugs directly to the arterial capillary bed of the tumor and release them in a controlled manner. This method lowers the systemic exposure to chemotherapeutics, while increasing their local concentration, thus resulting in greater tissue necrosis than classic trans-arterial chemoembolization (2).

TACE is indicated for patients with multinodular liver cancer without vascular invasion and extrahepatic diffusion (2). TACE is also strongly suggested for patients with unresectable liver primary tumor (HCC and cholangiocarcinoma) and chemo-resistant liver metastases, mainly from colorectal cancer carcinoma (CRC). HCC is the sixth most common cancer in the world and has a high mortality rate, being the third leading cause of cancer-related deaths worldwide (3). Cholangiocarcinoma incidence is increasing and, after HCC, is the most frequent liver primary cancer (4). Cholangiocarcinoma first-line treatment is surgery, when possible. Unresectable cholangiocarcinomas have a poor benefit with gemcitabine in combination with cisplatin or biologics (4).

Patients with liver metastases from any solid tumor have also a poor prognosis, especially if the metastases are unresectable. About 35% of patients with CRC have hepatic metastases (5). Surgery is still the standard first-line treatment of colorectal carcinoma liver metastases (CRC-LMs); however, only 20% of patients are candidates for radical resection (6). Unresectable CRC-LMs are treated with systemic chemotherapy, such as the combination of 5-fluorouracil with oxaliplatin and/or irinotecan, (7-10). Patients refractory to this combination hardly have a clinically significant tumor response to following chemotherapy lines; for this reason they are indicated for TACE (11, 12).

The technology of chemoembolization is constantly improving; in particular, a few months ago there was the launch of a new beads' formulation, the drug-elutable beads LifePearl® that can be loaded with irinotecan (LIFIRI®) or

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*Key Words:* LIFIRI®, LIFDOX®, liver metastases, chemoembolization, liver cancer, irinotecan, doxorubicin, polyethylene glycol drug-elutable beads.

with doxorubicin (LIFDOX®). The innovation of this product is its material, the polyethylene glycol (PEG), which makes the pearls more resilient to stress and attrition (<1% of damage during standard attrition testing). PEG is a hydrophilic material, which guarantees more compressibility, elasticity, while maximizing the time in suspension. In this way, the drug loaded stays longer in suspension and, also, the catheter deliverability is improved (13). Another innovation is the addition of sulfonate bonding (SPAc), which increases drug retention and release in the liver (13). The tighter calibration (100, 200, 400 μm diameter) of the beads result in a more controlled chemoembolization with optimized compressibility, thus allowing a precise and efficacious occlusion of capillary with lower risks of non-target chemoembolization.

The purpose of this study is to assess feasibility, tolerability, quality of life (QoL) and tumor response in every day real oncology after trans-arterial chemoembolization using polythylene glycol drug-eluting beads pre-charged with irinotecan (LIFIRI®) or with doxorubicin (LIFDOX®) for the treatment of primary and metastatic liver cancer.

## Patients and Methods

*Ethics*. The study was reviewed and approved by the Institutional Review Board. All patients signed informed written consent prior to study enrollment.

*Patients*. This was a retrospective cohort study of feasibility and tolerability, including 20 consecutive eligible patients who were treated with TACE using LifePearl® pre-charged with irinotecan (LIFIRI®) or with doxorubicin (LIFDOX®). Patients enrolled in the study fulfilled the following inclusion criteria: >18 years, histologically confirmed diagnosis of non-resectable primary or secondary liver cancer, no response or progression after previous lines of chemotherapy, Eastern Cooperative Oncology Group performance status (ECOG) 0-2, tumor size evaluable according to RECIST version 1.1 (14), good liver and renal functions (alanine aminotransferase and gamma-glutamyl transferase <three times the upper limit of normal levels, total bilirubin <2.5 mg/ml), good hematological values and life expectancy ≥3 months.

Patients were excluded from the data collection if: contraindicated to angiographic and selective visceral catheterization, had presence of significant extra hepatic disease, bad absorption, inflammatory intestinal disease, active infection, peripheral neuropathy ≥grade 2, pregnancy or breast feeding and other severe clinical impairment.

*Treatment plan*. Before TACE, an interventional radiologist monitored the arterial perfusion of the lesions with a diagnostic angiography that included selective celiac and superior mesenteric arteriograms. The following step of the pre-treatment evaluation was to minimize any type of chemotherapy extra-hepatic perfusion. Extra-hepatic leakage blockade was performed using a distal catheter. LIFIRI® and LIFDOX® treatment involved the infusion of 2 ml of LifePearl® (Terumo Europe NV, Leuven, Belgium) loaded with irinotecan (100 mg) and doxorubicin (50 mg), respectively. Drug type was selected according to cancer type: primary liver cancer or metastases. A second LIFIRI® or LIFDOX® was repeated after 30 days, as previously reported based on our experience with chemoembolization (15). The loaded pearls were mixed with 5 ml of non-ionic contrast solution and 5 ml of distilled water to guarantee correct volume of infusion.

The infusion lasted 10-12 min (median infusion speed of 1 ml/minute) checking the beads' distribution continuously.

Support therapy, including antibiotics (ceftazidime 1,000 mg twice a day for 72 h), antiemetic prophylaxis (ondansentron 10 mg before and 6 hours after TACE), dexamethasone (12 mg before TACE) and intravenous hydration (1,500 ml of glucose saline solution for 72 hours), was used to stabilize transaminases' levels and to prevent infections (16). One vial of 10 mg morphine was administered before TACE and 6 hours after chemoembolization. Ranitidine 50 mg was used for gastric protection. Lidocaine 2%, 4 ml (80 mgr), was adopted as intra-arterial medication.

*Efficacy and tolerability*. Safety was monitored according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 3.0, whereas the Response Evaluation Criteria in Solid Tumors (RECIST) criteria version 1.1 was used for tumor response. Abdomen and pelvis computed tomography (CT) scan was performed within 1, 3, 6 and 9 months from the treatment completion according to RECIST indications (14, 17, 18).

*Tumor response*. Tumor response was assessed with the EASL method, which was a measure based on tumor progression in respect to change in necrosis (19). Initial values of greatest diameter of viable tumor against greatest total tumor diameter were compared with those observed after each chemoembolization.

*Quality of life (QoL)*. QoL was measured using the scale of Edmonton (20). Our hypothesis was that patients would have better physical and social characteristics, as well as better health perception one month after chemoembolization.

*Statistical analysis*. Data of the whole sample (n=20) were analyzed and continuous data were reported as mean±standard deviation. Proportions were expressed in percentage. Chi-square and Student's *t*-test were used to assess significance of continuous variables ($p<0.05$).

## Results

*The sample*. From May to October 2015, two Italian centers enrolled 20 patients in the present study, 14 (70%) were male and 6 (30%) female, with a median age of 64 years (range=45-83); 80% of the sample had ECOG=0. All patients had increased levels for alpha fetoprotein in HCC, carcinoembryonic antigen (CEA) in liver metastases from colorectal cancer and carbohydrate antigen CA 15-3 in breast cancer, none in uveal melanoma, while 60% had values more than 10-times the upper limit range. Each patient was treated with LIFIRI® or LIFDOX®, 16 patients (80%) received the planned 2 cycles of TACE, 4 (20%) received only one cycle.

Ten patients (50%) were affected by HCC, 4 (20) by cholangiocarcinoma, 4 (20%) by CRC-LM, 1 (5%) by liver

Table I. *Non-HCC characteristics*.

| ID | Gender | Year | Disease | Method | Drug | Drug concentration (mg) | Size of beads (μm) | Tumor response | Procedure complications |
|---|---|---|---|---|---|---|---|---|---|
| 1 | f | 75 | CHOLANGIO | LIFDOX® | Doxo | 50 | 100±25 | PR | None |
| 2 | m | 67 | CHOLANGIO | LIFDOX® | Doxo | 50 | 100±25 | CR | None |
| 7 | f | 61 | U-LM | LIFIRI® | Irinotecan | 100 | 100±25 | CR | None |
| 8 | m | 63 | CRC-LM | LIFIRI® | Irinotecan | 100 | 200±25 | PR | None |
| 12 | f | 64 | CHOLANGIO | LIFDOX® | Doxo | 50 | 100±25 | CR | None |
| 15 | m | 45 | BC-LM | LIFIRI® | Irinotecan | 100 | 100±25 | PR | None |
| 17 | f | 67 | CHOLANGIO | LIFDOX® | Doxo | 50 | 400±50 | PR | None |
| 18 | f | 45 | CRC-LM | LIFIRI® | Irinotecan | 100 | 400±50 | CR | None |
| 19 | m | 55 | CRC-LM | LIFIRI® | Irinotecan | 100 | 400±50 | PR | None |
| 20 | m | 64 | CRC-LM | LIFIRI® | Irinotecan | 100 | 400±50 | PR | None |

HCC, Hepatocellular carcinoma; CHOLANGIO, cholangiocarcinoma, BC-LM, breast cancer liver metastases; CRC-LM, colorectal carcinoma liver metastases; U-LM, uveal liver metastases; doxo, doxorubicin; CR, complete response; PR, partial response; LIFIRI®, TACE with Lifepearls® pre-loaded with irinotecan; LIFDOX®, TACE with Lifepearls® pre-loaded with doxorubicin.

Table II. *HCC characteristics*.

| ID | Gender | Year | Disease | Method | Drug | Drug concentration (mg) | Size of beads (μm) | Tumor response | Procedure complications |
|---|---|---|---|---|---|---|---|---|---|
| 3 | m | 70 | HCC | LIFDOX® | Doxo | 50 | 300±25 | CR | None |
| 4 | f | 83 | HCC | LIFDOX® | Doxo | 50 | 200±25 | CR | None |
| 5 | m | 61 | HCC | LIFDOX® | Doxo | 50 | 200±25 | PR | None |
| 6 | m | 65 | HCC | LIFDOX® | Doxo | 50 | 200±25 | CR | None |
| 9 | m | 63 | HCC | LIFDOX® | Doxo | 50 | 100±25 | PR | None |
| 10 | m | 74 | HCC | LIFDOX® | Doxo | 50 | 300±25 | CR | None |
| 11 | m | 64 | HCC | LIFDOX® | Doxo | 50 | 300±25 | CR | None |
| 13 | m | 55 | HCC | LIFDOX® | Doxo | 50 | 200±25 | CR | None |
| 14 | m | 64 | HCC | LIFDOX® | Doxo | 50 | 200±25 | PR | None |
| 16 | m | 83 | HCC | LIFDOX® | Doxo | 50 | 400±50 | PR | None |

HCC, Hepatocellular carcinoma; CHOLANGIO, cholangiocarcinoma, BC-LM, breast cancer liver metastases; CRC-LM, colorectal carcinoma liver metastases; U-LM, uveal liver metastases; doxo, doxorubicin; CR, complete response; PR, partial response; LIFIRI®, TACE with Lifepearls® pre-loaded with irinotecan; LIFDOX®, TACE with Lifepearls® pre-loaded with doxorubicin.

metastases from breast cancer (BR-LMs) and 1 (5%) from uveal melanoma (U-LM) (Tables I and II).

Irinotecan (100 mg) was used for the treatment of liver metastases, whereas doxorubicin (50 mg) was used for HCC and cholangiocarcinoma therapy; the sizes of LifePearl® are reported in Table I.

*Tolerability*. Median hospitalization for chemoembolization was 48 hours (range=24-72). We observed no complications during the chemoembolization procedure that was well-tolerated by all patients treated. No abdominal pain was recorded; however, there was complaining during the injection, as previously observed with beads.

Two patients (10%) showed adverse events after TACE and reported grade 2 adverse reactions, mainly pain at upper right quadrant of abdomen. Post-embolic syndrome was the main side-effect observed as a consequence of 10% of TACE. Other treatment-related events included mild gastritis in 3 (15%) patients, dehydration (G2) in 1 (5%) patient. These side-effects, however, were resolved without complications. These symptoms were probably related to the post-embolization syndrome (PES) and were of mild intensity. Elevation of liver enzymes occurred almost in every patient, probably due to the extensive type of embolization performed.

*Tumor response*. Overall response rate was high, >80% in most patients with 63% of complete response (CR) and 37% of partial response (PR) at one month after therapy. CR, in particular, was observed in 60% of HCC, 50% of cholangiocarcinoma and 25%

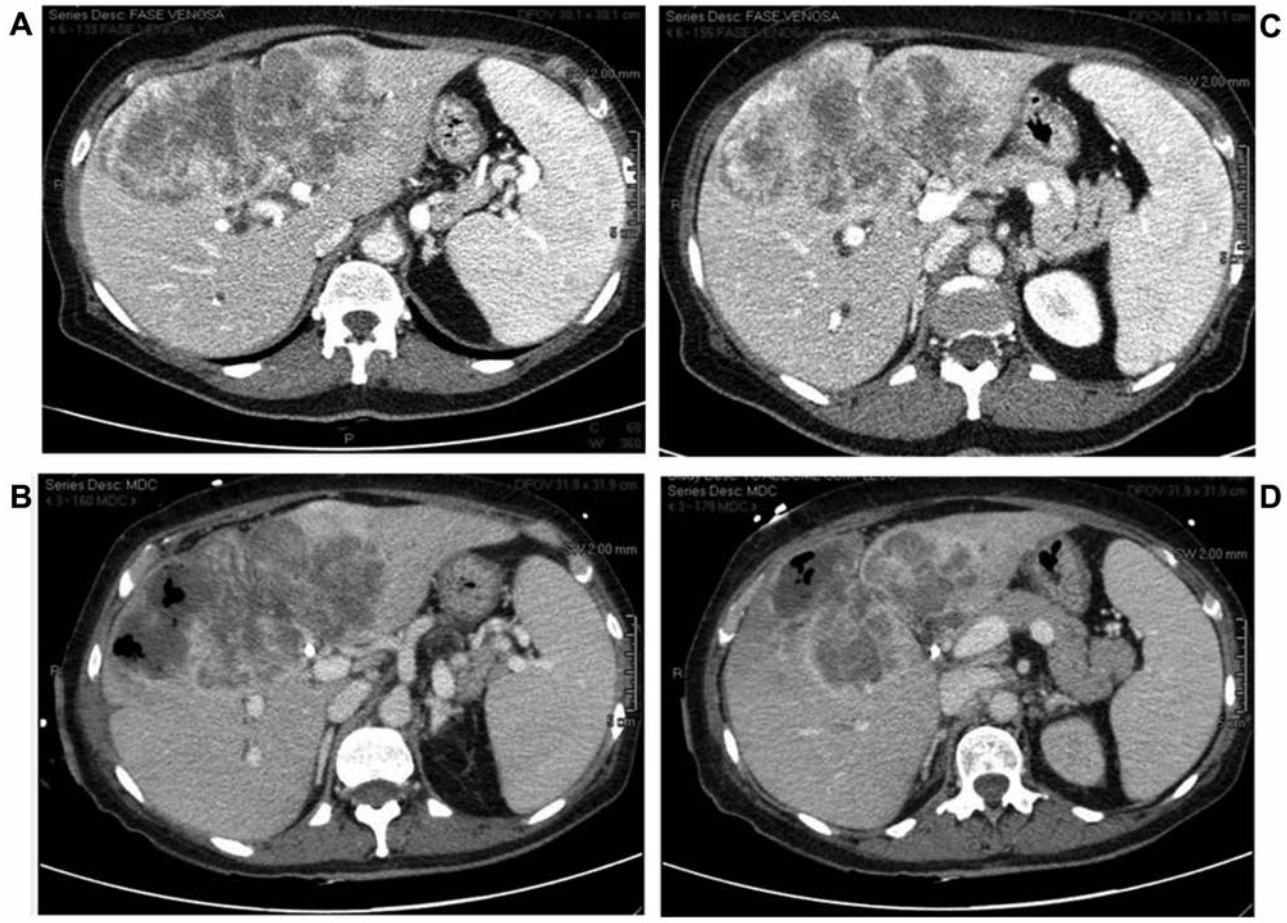


Figure 1. *CT scan of venous phase. A, C: pre-TACE; B, D: 30 days after TACE. Note the significant reduction of tumor vascularization and wide area of necrosis with gas bubbles inside due to infection in cholangiocarcinoma (patient 17).*

of CRC-LMs. Liver metastases from uvea showed CR, whereas metastases from breast cancer had PR (Table III). Each patient, moreover, showed a >50% reduction of alpha fetoprotein and CEA levels after 1 month of treatment.

In relation to tumor size, a modest maximum diameter reduction (25% on average) in metastatic disease was observed; this reduction was of 50% in HCC. An increase of necrosis in 50% of metastatic disease and 75-100% of HCC was also recorded.

During the 3-to-6-month follow-up, no increase in tumor maximum diameter of HCC was observed; however, it was seen in 40% of metastatic disease.

The analysis of vascular imaging showed the disappearance of contrast medium uptake in all HCC cases and a decrease of 50% of uptake in metastatic disease (Figure 1).

*QoL*. QoL analysis at 1 month after treatment showed that physical and social functioning were improved in most of patients. Patients also expressed a better health perception.

## Discussion

Surgery may not be possible for several cases of HCC, cholangiocarcinoma and CRC-LM. For this reason patients are treated with first-line chemotherapy. The indication of second-line systemic treatment is still under discussion, whereas the locoregional treatment of primary and secondary liver cancer is, nowadays, very diffuse and involves several methodologies, including hepatic arterial infusion pumps for CRC-LM (21), implantable infusuports (22) and classical TACE (23). The purpose and efficacy of intra-arterial infusion are well known (increase of drug concentrations inside the tumor and decrease of systemic leakage); however, particular attention must be paid to possible serious adverse events, which may lead to biliary sclerosis, gastric lumens dislodgement and/or misplacement of catheter leading to systemic leakage (21, 22).

The technological improvements of the chemoembolization method, especially the introduction of irinotecan-pre-loaded DC Beads, showed good results in HCC. For this reason,

Table III. *Tumor response*.

| | N | % | CR | % | PR | % |
|---|---|---|---|---|---|---|
| HCC | 10 | 50 | 8 | 80 | 2 | 20 |
| CHOLANGIO | 4 | 20 | 2 | 50 | 2 | 50 |
| CRC-LM | 4 | 20 | 1 | 25 | 3 | 75 |
| U-LM | 1 | 5 | 1 | 100 | 0 | 0 |
| BC-LM | 1 | 5 | 0 | 0 | 1 | 100 |

HCC, Hepatocellular carcinoma; CHOLANGIO, cholangiocarcinoma, BC-LM, breast cancer liver metastases; CRC-LM, colorectal carcinoma liver metastases; U-LM, uveal liver metastases; CR, complete response; PR, partial response.

TACE was applied also to CRC-LMs showing good patients' compliance and acceptance. This method is more precise and allows the reduction of systemic side-effects as reported by *in vitro* and *in vivo* studies (24-26), avoiding the problems and disadvantages of cumbersome methods, such as placing pumps with open laparatomy.

Further improvements of TACE include sustained exposure to new toxic agents and the development of new beads that are more chargeable and biocompatible. Among the new beads, LifePearl® present certain advantages, such as better calibration (diameter range), higher resilience to stress and attrition, maximized time in suspension, better catheter deliverability, more controlled chemoembolization with uniform and distal distribution allowing a precise and efficacious occlusion of capillary with lower risks of non-target chemoembolization. These pearls have been recently released but, currently, there are no published data on their application. For this reason, we decided to perform this study. We applied these pre-loaded with irinotecan or with doxorubicin pearls to 20 patients and report the first results on efficacy and short-term tolerability.

Previous studies on the efficacy of TACE for the treatment of CRC-LMs have showed response rates of about 60-75% (15, 24-28). We observed 25% of CR and 75% of PR in patients affected by CRC-LMs one month after the LIFIRI®.

Recent results using different types of drug-eluting beads, LC Beads loaded with doxorubicin (DEBDOX), doxorubicin-eluting Quadra Spheres (hqTACE) and conventional TACE for the treatment of HCC, showed that the above methodologies had similar efficacy. Tumor response was 65% for conventional TACE, 64% for DEBDOX and 54% for hqTACE (28). Our results are in agreement with these findings as we observed a 60% of CR and 40% of PR in HCC one month after LIFDOX®.

A recent review on locoregional therapy of intrahepatic cholangiocarcinoma, including radiofrequency ablation (RFA) and TACE, showed interesting results on efficacy and tolerability. TACE increased progression-free survival and overall survival when compared to oxaliplatin and gemcitabine (29). In our unit, we treated 4 cholangiocarcinoma patients with LIFEDOX® and observed 2 CRs and 2 PRs, suggesting that this approach may be potentially effective for cholangiocarcinoma as well.

Treatment of liver metastases from breast cancer with TACE has been shown to improve response rate and overall survival when compared to systemic chemotherapy. We had only one case of liver metastases from breast cancer; however, TACE results showed a partial response with >80% of tumor reduction, in agreement with previous studies (30). Concerning the results on the complete response observed in the patient with liver metastases from uveal melanoma (UM-LM), they were also in agreement with our previous findings, when we treated 10 UM-LM patients with TACE using DC Beads, reporting a >60% of tumor reduction (range=60-90%) (31). Future work is needed with a larger sample to confirm these data.

No severe general drug-related side-effects were observed as a consequence of LIFIRI® or LIFDOX®. PES, hypertension, nausea and pain were the most reported side-effects. Our safety results are in agreement with those of our previous studies, which included PES, pain, nausea and vomiting.

In relation to QoL, data analysis showed an improvement of physical and social functioning, as well as better health perception one month after chemoembolization. This result was in agreement with previous data on QoL using the DC Beads, thus suggesting that LifePearl® are non-inferior in terms of QoL compared to previously marketed products.

Main limitations of this study are the small number of patients and the short period of observation. Further studies with a larger number of patients are required to assess long-term efficacy and safety.

Nevertheless, our results are important because this is the first report on the application of chemoembolization with LifePearl® pre-loaded with irinotecan or with doxorubicin as second-line therapy of unresectable primary and secondary liver cancer. We observed good feasibility and tolerability of the procedure and similar results were obtained as with other beads using the same pre-medication therapy. Another important advantage of LifePearl® is their longer time of suspension, hence avoiding their precipitation. The LifePearl® approach by an expert medical staff seems to be a step forward for simplifying TACE and could be combined with biological agent (32).

## Conclusion

LifePearl® pre-loaded with irinotecan (LIFIRI®) or doxorubicin (LIFDOX®) can be a step closer in the chemoembolization field for the treatment of both primary and secondary liver cancer with promising results on good tumor response and low levels of toxicity. Future work is needed for confirmation of these data.

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