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CLINICAL INVESTIGATION

Hepatic Arterial Chemoembolization Using Drug-Eluting Beads in Gastrointestinal Neuroendocrine Tumor Metastatic to the Liver

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Abstract
Purpose This study was designed to evaluate short (<3 months) and intermediate-term (>3 months) follow-up in patients with metastatic neuroendocrine tumor to the liver who underwent hepatic arterial chemoembolization with drug-eluting beads at a single institution.
Methods Institutional review board approval was obtained for this retrospective review. All patients who were treated with 100–300 or 300–500 μm drug-eluting LC Beads (Biocompatibles, UK) preloaded with doxorubicin (range, 50–100 mg) for GI neuroendocrine tumor metastatic to the liver from June 2004 to June 2009 were included. CT and MRI were evaluated for progression using Response Evaluation Criteria In Solid Tumors (RECIST) or European Association for the Study of the Liver (EASL) criteria. Short-term (<3 months) and intermediate-term (>3 months) imaging response was determined and Kaplan–Meier survival curves were plotted.
Results Thirty-eight drug-eluting bead chemoembolization procedures were performed on 32 hepatic lobes, comprising 21 treatment cycles in 18 patients. All procedures were technically successful with two major complications (biliary injuries). At short-term follow-up (<3 months), 22 of 38 (58%) procedures and 10 of 21 (48%) treatment cycles produced an objective response (OR) with the remainder having stable disease (SD). At intermediate-term follow-up (mean, 445 days; range, 163–1247), 17 of 26 (65%) procedures and 8 of 14 (57%) treatment cycles produced an OR. Probability of progressing was approximately 52% at 1 year with a median time to progression of 419 days.
Conclusions Drug-eluting bead chemoembolization is a reasonable alternative to hepatic arterial embolization and chemoembolization for the treatment of metastatic neuroendocrine tumor to the liver.

Keywords Embolization · Chemoembolization · Carcinoid · Liver · Neuroendocrine tumor

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Introduction

Neuroendocrine tumors arise from cells that release serotonin and other vasoactive substances that can precipitate carcinoid syndrome, including episodic flushing, wheezing, diarrhea, and eventually heart valve dysfunction. They are most frequently found in the gastrointestinal tract and bronchi. Of gastrointestinal (GI) neuroendocrine tumors, the vast majority arise from the foregut or midgut [20, 21, 26, 27, 37, 39, 42].

Most GI neuroendocrine tumors are malignant but follow a more indolent course [3]. The majority of small bowel and colon neuroendocrine tumors present with

lymph node and liver metastases with <10% experiencing carcinoid syndrome [21]. The median overall survival duration is 75 months [42].

Multiple treatment modalities have been explored to treat metastatic neuroendocrine tumors, engaging gastroenterologists, oncologists, surgeons, diagnostic radiologists, and interventional radiologists. Treatment with somatostatin analogues has become the standard of care for palliation of symptoms and has been shown to lengthen the time to tumor progression [33]. Systemic chemotherapy provides variable results, and tumor regression is observed in <30% [21, 28, 30, 34]. Although limited data exist regarding surgical resection, a 2006 retrospective review showed improved survival and symptom relief from surgical cytoreduction versus hepatic arterial embolization [31]. A similar study showed a survival benefit with surgery relative to embolization or medical management, but no difference in symptom improvement was observed [29].

Surgical and/or medical management cannot be employed in a significant number of patients secondary to tumor bulk or unfavorable biologic conditions. Both hepatic arterial embolization and chemoembolization are accepted methods of palliative treatment in these patients. Numerous studies have demonstrated symptomatic improvement and tumor regression with both methods [1, 4, 6, 7, 9–12, 14–17, 19, 22, 24, 25, 35, 36, 38, 41]. Debate exists within the interventional radiology literature regarding the use of embolization versus chemoembolization. A 2007 retrospective study showed a trend toward prolonged time to progression with chemoembolization but was not statistically significant. No difference in toxicity was noted between the two groups [36]. More recently, yttrium-90 (Y90) radioembolization has emerged as an alternative to chemoembolization for the treatment of metastatic GI neuroendocrine tumor. The technique employs microspheres embedded with radioactive Y90 designed to emit radiation at a specific half-life and activity. Initial studies have demonstrated tumor response rates and survival times comparable to bland embolization and chemoembolization [32].

At our institution, patients with metastatic GI neuroendocrine tumor were treated with hepatic arterial chemoembolization, bland embolization, or radioembolization until 2005. Beginning in 2004, we changed our chemoembolization regimen exclusively to doxorubicin-impregnated drug-eluting beads.

Drug-eluting beads are produced from a biocompatible polyvinyl alcohol (PVA) hydrogel that has been altered to allow loading with the chemotherapeutic agents, doxorubicin or irinotecan. Preliminary data have been published regarding the use of drug-eluting beads for hepatocellular carcinoma (HCC) and metastatic colorectal carcinoma (mCRC) [13, 40]. Preliminary results in a recent prospective study by de Baere et al. suggest that beads impregnated with doxorubicin were effective in the short-term (<3 months) in a cohort of 20 patients with GI neuroendocrine metastases to the liver [5]. In the present study, we retrospectively reviewed the outcomes of patients with GI neuroendocrine metastases to the liver treated with doxorubicin impregnated LC Beads (Biocompatibles, United Kingdom) at our institution. The primary endpoint was tumor response by Response Evaluation Criteria In Solid Tumors (RECIST) or European Association for the Study of the Liver (EASL) criteria 3 months after completion of a treatment cycle of drug-eluting bead chemoembolization. The secondary endpoint was tumor response by RECIST or EASL in intermediate-term follow-up (>3 months) after the completion of a treatment cycle.

Materials and Methods

Institutional Review Board approval was obtained for this HIPAA-compliant retrospective review. Our interventional radiology database was queried for all patients treated with drug-eluting bead chemoembolization between June 2004 and June 2009. Inclusion criteria included: (1) history of metastatic GI neuroendocrine tumor to the liver, (2) treatment with drug-eluting bead chemoembolization, (3) preprocedure contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI), (4) <3 month postprocedure contrast-enhanced CT or MRI, and (5) prior consent for use of medical records for research purposes.

The electronic medical record (EMR) was used to extract demographic, clinical, laboratory, and procedural data. All enhanced CT and MRI images were evaluated from the study period. Liver function tests and chromogranin A levels were compared before and immediately after drug-eluting bead chemoembolization when available. The EMR was searched to determine which patients had undergone prior chemoembolization without drug-eluting beads or previous surgical resection, and these patients were excluded. The length of hospital stay was determined and complications compiled.

All drug-eluting bead chemoembolizations were performed using a standard technique. After visceral angiography, the right or left proper hepatic artery was selected using coaxial technique. 100–300 or 300–500 μm LC Beads (Biocompatibles) preloaded with doxorubicin (range, 50–100 mg) by the hospital pharmacy were infused into the most selective artery possible. A "procedure" was defined as one patient encounter (chemoembolization of one or both lobes), whereas a "treatment cycle" was comprised of all procedures required to complete treatment of the tumor-bearing portion of the liver [2]. On two occasions, both hepatic lobes were super-selectively

embolized during the same procedure; most patients underwent sequential drug-eluting bead chemoembolization of each lobe at separate procedures. Initially, embolization endpoint was defined as "near stasis" where contrast cleared from the respective artery within three heartbeats. Approximately midway through the study period, the operator modified the procedure end point and terminated the procedure when a pruned-tree appearance was reached. Choice of bead size depended on the size of the overall tumor volume. For small tumor volumes (<3 cm), 100–300 μm beads were used; for larger tumor volumes, 300–500 μm beads were used. The dosage of doxorubicin infused was dependent on the angiographic endpoint and ranged from 50–100 mg.

Available pre- and post-procedural imaging studies were evaluated by a board-certified radiologist and data stored in an electronic database. Tumor response was assessed for each procedure and treatment cycle using all imaging data available through February 2009, and tumor size and enhancement were assessed to conform to RECIST and EASL criteria (Table 1).

Objective response (OR) was defined for a specific hepatic lobe or patient as complete response (CR) or partial response (PR) by RECIST or EASL criteria. For example, a patient with stable disease (SD) by RECIST criteria but PR by EASL criteria was considered to have an OR. Conversely, a nonresponder was a patient who had progressive disease (PD) or SD by both RECIST and EASL.

A Kaplan–Meier plot was generated for the survival of patients in intermediate-term using time to progression in days and the probability of progression was assessed at various time points.

Results

Eighteen patients (10 men, 8 women) met inclusion criteria with mean age of 57 (range, 42–76) years. Thirty-eight drug-eluting bead chemoembolization procedures were performed on 32 hepatic lobes in 18 patients comprising 21 treatment cycles. The range of doxorubicin used in each procedure was 50–100 mg. Total dose ranged from 100–300 (mean, 165) mg. A dosage of 100–300 μm beads were used in 14 procedures and 300–500 μm beads in 24 procedures. Finally, four patients underwent chemoembolization with drug-eluting beads and an additional embolic agent: either Contour SE microspheres (Boston Scientific, Natick, MA) or Embospheres (Biosphere Medical, Rockport, MD).

Short-term (<3 months) imaging follow-up was available for 38 procedures and 21 treatment cycles in 18 patients for an average of 59 days. No procedures lead to progression by imaging criteria during short-term follow-up. Twenty-two procedures (58%) and ten treatment cycles (48%) produced an objective short-term response, with the remainder having stable disease (Fig. 1A, B).

Intermediate-term (>3 months) imaging follow-up was available for 26 procedures and 14 treatment cycles in 14 patients for an average of 445 days (range, 163–1247; standard deviation, 326). Of the 26 procedures, 17 (65%) produced an objective response to drug-eluting bead chemoembolization, whereas the remainder were nonresponders (Fig. 2A). Of the 14 treatment cycles, 8 (57%) produced an objective response, whereas the remainder were nonresponders (Fig. 2B). Kaplan–Meier plots demonstrate that the probability of progression by RECIST or EASL was 52% (19, 77%) at 1 year, with a median time to progression of 419 days (Fig. 3).

All treatments were technically successful. Each patient was admitted for overnight observation; two required an additional hospital day for pain control and mild hypertension, respectively. Two major complications occurred. After right lobe drug-eluting bead chemoembolization (100 mg of doxorubicin in 300–500 μm drug-eluting beads) with 500–700 μm Contour SE particles, a 54-year-old woman with a previous left hepatectomy presented to the emergency department with severe right upper quadrant pain. An enhanced-CT of the abdomen showed a wedge-shaped perfusion abnormality in the posterior segment of the right lobe, in addition to intrahepatic biliary dilatation. This led to percutaneous transhepatic cholangiography and internal/external biliary stent placement. The patient

Table 1 Imaging criteria for evaluating tumor response

	RECIST	EASL
Complete response (CR)	Disappearance of all target lesions	Complete absence of enhancing areas within target lesions
Partial response (PR)	>30% decrease in sum of longest diameter of target lesions	>50% decrease in enhancing areas within target lesions
Stable disease (SD)	Does not meet criteria for PR or PD	Does not meet criteria for PR or PD
Progressive disease (PD)	>20% increase in sum of longest diameter of target lesions OR new lesions	>25% increase in diameter of one or more tumors OR new lesions
Objective response (OR)	CR or PR	CR or PR

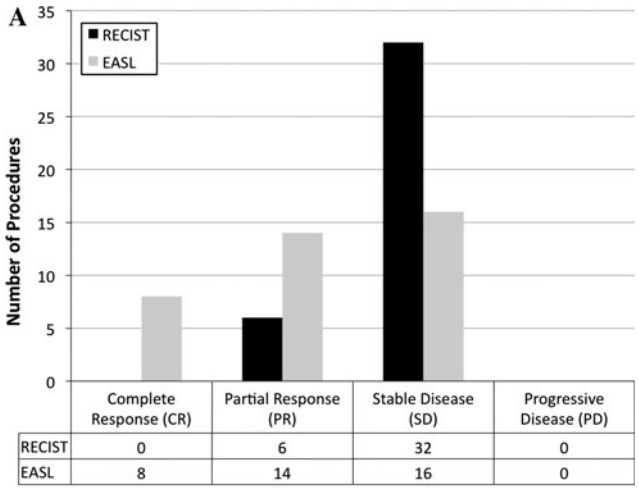

Fig. 1 Short-term (<3 months) response to DEB-HACE. **A** Response to individual procedures. **B** Response to treatment cycles

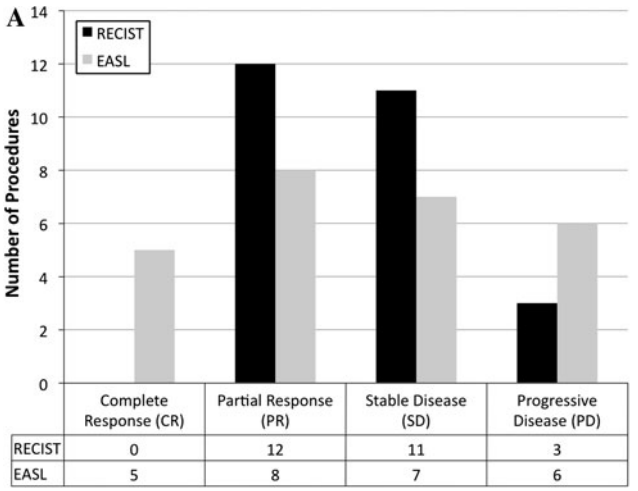

Fig. 2 Intermediate-term (>3 months) response to DEB-HACE. **A** Response to individual procedures. **B** Response to treatment cycles

subsequently did well, and the biliary tube was removed without complication. At 501 days after chemoembolization, her disease was classified as an objective response. The other complication was biliary injury noted on routine follow-up CT in a 57-year-old woman, which did not require additional treatment.

Two patients died during the study period from progressive disease. Both were included in the statistical analysis based on their available imaging.

Discussion

Eighteen patients who underwent a total of 21 treatment cycles met inclusion criteria for our study. On short-term follow-up, 48% of treatment cycles led to an objective response; on intermediate-term follow-up, 57% led to an objective response. The median time to progression was 419 days. To our knowledge, the data presented by de Baere et al. is the only preliminary data available about the treatment of GI neuroendocrine metastases to the liver with drug-eluting bead chemoembolization. The preliminary results demonstrate an 80% partial response by RECIST at 3 months follow-up in 20 patients, suggesting that drug-eluting beads represent a viable treatment strategy in the short-term. In 1998, M.D. Anderson published their experience with self-manufactured microencapsulated cisplatin in 18 patients with metastatic neuroendocrine tumors. Ten exhibited objective response (by RECIST criteria) on short-term imaging, whereas the remainder had stable disease [8]. Together, these preliminary studies demonstrate an initial proof of concept for the treatment of metastatic carcinoid tumors with drug-eluting bead chemoembolization.

Studies have shown a difference between carcinoid tumors and islet cell tumors regarding symptom and imaging response after embolization and chemoembolization. Gupta et al. demonstrated a statistically significant

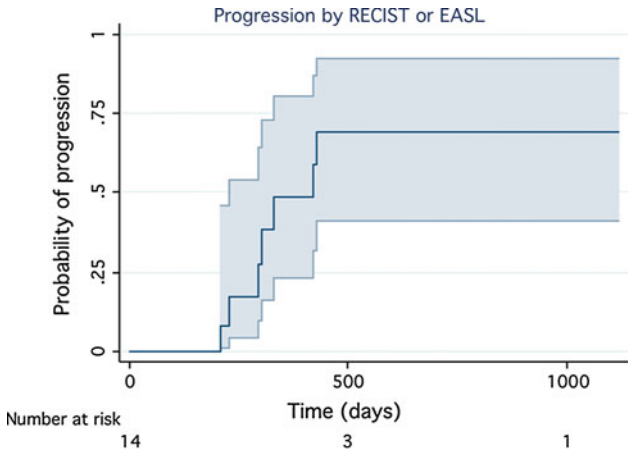

Fig. 3 Kaplan–Meier survival curve demonstrating probability of progression over time

improvement in imaging response with embolization relative to chemoembolization for GI neuroendocrine tumors but prolonged survival and response rate with chemoembolization for islet cell tumors [15].

Although some published data have indicated improved response with embolization compared with chemoembolization in patients with GI neuroendocrine tumor, Ruutiainen et al. have shown trends toward improved symptom relief and statistically significant improved time to progression with chemoembolization relative to embolization [36]. It is unclear whether this discrepancy is related to differences in the biology of the studied cohorts or technical differences at each institution.

More recently, yttrium-90 (Y90) radioembolization has emerged as an alternative to chemoembolization for the treatment of GI neuroendocrine tumor metastatic to the liver. Initial reports suggest that Y90 radioembolization results in comparable tumor response, side-effect profile, and median survival time to that of bland and chemoembolization (Table 2). In particular, an open-label, multicenter, phase II study has demonstrated a 43% objective response rate at 6 months posttreatment and median survival time of 28 months in 23 patients who underwent lobar Y90 radioembolization for the treatment of GI neuroendocrine metastases to the liver [32].

Our data indicate that chemoembolization with doxorubicin-impregnated LC Beads may be a reasonable alternative to embolization, standard chemoembolization, and radioembolization for the treatment of GI neuroendocrine tumors metastatic to the liver. Data from this retrospective review compare favorably with prior reports regarding objective response on imaging at 1-year follow-up.

This study shows an objective response in 48% (10/21 treatment cycles) at short-term follow-up compared with 67% in the M.D. Anderson data (69 patients), 46% in the University of Washington study (46 patients), and 80% in the de Baere et al. study (20 patients; Table 2). At intermediate-term follow-up, the present study demonstrates an objective response in 57% (8/14 treatment cycles) with 43% (6/14) nonresponders. Although our response rate falls within the range of previously published results, it may have been impacted by differences in procedure and our small sample size.

Gupta et al. report a time to progression (TTP) of 22.7 months, in 81 patients who underwent embolization or chemoembolization [15]. Ruutiainen et al. report a TTP of 10 and 55 months for embolization and chemoembolization, respectively [36]. De Baere et al. report a median TTP of 15 months. Our median TTP (14 months) is near the lower end of this range but may have been impacted by our small study size.

Table 2 Comparison of objective response and median time to progression for embolization, chemoembolization, radioembolization, and drug-eluting bead chemoembolization in recently published studies

Study parameters				Imaging criteria				Median time to progression (TTP)
Medical center	Tumor type	Year	Treatment		OR	SD	PD	
M.D. Anderson	GI NET	2005	HAE/HACE	RECIST	67%	24%	8%	22.7
Univ. Pennsylvania	NET	2007	HAE	RECIST	[a]	[a]	[a]	10
Univ. Pennsylvania	NET	2007	HACE	RECIST	[a]	[a]	[a]	55
Washington University	GI NET	2007	HAE/HACE	RECIST	46%	32%	23%	20[b]
Institut Gustave Roussy	GI NET	2008	DEB-HACE	RECIST	80%	15%	5%	15
Multi-center	GI NET	2008	Y90	RECIST	43%	52%	5%	22-28[c]

[5, 15, 17, 32, 36]

[a] Data not available for GI NET only

[b] Progression free survival (PFS)

[c] Median survival

Drug-eluting beads may offer some advantages to traditional embolization, chemoembolization, and radioembolization. Previous studies have demonstrated that the pharmacokinetics of chemotherapy delivery trend toward controlled release in beads similar to the ones used in this study [23]. Because lipiodol is not used, tumor size and viability is more easily evaluated on follow-up imaging. Although procedural toxicity was not extensively evaluated in this review, only a single patient experienced a major complication that required an elevated level of care, and our 30-day mortality rate of 0% is below the rates reported in previous data. Nearly all patients were discharged from the hospital the day after the procedure versus an average of 1.5 hospital days in the literature [36]. More recently, chemoembolization has emerged as part of a combination therapy with radiofrequency ablation for patients with hepatocellular carcinoma [18]. The combination therapy does not appear to be beneficial for smaller lesions (<3 cm) but does demonstrate synergy with larger, hypervascular lesions. At our institution, we have not explored combining drug-eluting bead chemoembolization with radiofrequency ablation for patients with metastatic neuroendocrine tumors, but it may emerge as an option for patients with increased tumor burden who do not qualify for chemoembolization alone.

However, drug-eluting beads do have a significant cost. Drug-eluting bead chemoembolization is nearly five times the cost of chemoembolization, and although the new technology does compare favorably with traditional therapy, the data presented in this study warrant a cost-benefit analysis that reassesses our institution's preference. However, without a prospective, randomized trial that directly compares drug-eluting beads to chemoembolization or newer approaches, such as Y90 radioembolization, a complete reversion to traditional chemoembolization may be premature.

This study has a few limitations. First, the retrospective nature and small sample size limit generalizability of the data. The size of the drug-eluting beads and embolization endpoint was not uniform across all procedures, which could introduce variability into the results. Using imaging as the sole endpoint accentuates the limitations of these criteria to accurately match the disease biology after chemoembolization. For example, tumor death and subsequent necrosis may take months before becoming visible on enhanced CT or MRI. Additionally, RECIST criteria focus solely on tumor size and ignore enhancement as a surrogate for tumor viability. Although EASL improves on this limitation, the frequency of disagreement between RECIST and EASL (Figs. 1, 2) suggests that a more rigorous, generalizable set of criteria (including toxicity) may need to be adopted to ensure accurate scoring of treatment response.

Conclusions

Despite limitations with the current study, hepatic arterial chemoembolization with doxorubicin-eluting beads was safe and tolerable for nearly all patients. Median time to progression and response rate for drug-eluting bead chemoembolization appears to compare favorably with previously reported data for embolization and chemoembolization for the treatment of GI neuroendocrine tumor metastatic to the liver. The preliminary data in the literature warrant a more rigorous, prospective comparison of embolization, chemoembolization, radioembolization, and drug-eluting bead chemoembolization.

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Conflict of interest The authors declare that they have no conflicts of interest.

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